PB80-183197

Investigation of Selected Potential Environmental Contaminants: Epoxides

Syracuse Research Corp., NY

Prepared for

Environmental Protection Agency
Washington, DC

Mar 80

U.S. Department of Commerce
National Technical Information Service
NTIS

PB80-183197

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SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA
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1. REPORT NO. EPA-560/11-80-005	2.	3. RECIPIENT'S ACCESSION NO. PB80 183197
4. TITLE AND SUBTITLE Investigation of Selected Potential Environmental Contaminants: Epoxides		5. REPORT DATE March 1980 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Dennis A. Bogyo, Sheldon S. Lande, William M. Meylan, Philip H. Howard, Joseph Santodonato		8. PERFORMING ORGANIZATION REPORT NO TR 80-535
9. PERFORMING ORGANIZATION NAME AND ADDRESS Center for Chemical Hazard Assessment Syracuse Research Corporation Merrill Lane Syracuse, New York 13210		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO. EPA 68-01-3920
12. SPONSORING AGENCY NAME AND ADDRESS Office of Toxic Substances U.S. Environmental Protection Agency Washington, D.C. 20460		13. TYPE OF REPORT AND PERIOD COVERED Final Technical Report 14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This report reviews the potential environmental and health hazards associated with the commercial use of selected epoxide compounds. Four commercial compounds are discussed in the report: ethylene oxide - primarily used as a chemical intermediate; propylene oxide - primarily used as a chemical intermediate; butylene oxide-primarily used as a stabilizer for chlorinated solvents; and diepoxybutane - primarily used as a specialty chemical. Data on physical-chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination, as well as information related to human health and biological effects, are reviewed and evaluated.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
ethylene oxide propylene oxide butylene oxide diepoxybutane	epoxides toxicity production commercial use chemistry environmental fate	

18. DISTRIBUTION STATEMENT Document is available to the public through the National Technical Information Service Springfield, VA 22151	19. SECURITY CLASS *(This Report)* 20. SECURITY CLASS *(This page)*	21. NO. OF PAGES 22. PRICE

EPA Form 2220-1 (9-73)

EPA-560/11-80-005 TR 80-535

INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS:

EPOXIDES

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March 1980
FINAL REPORT

Contract No. 68-01-3920
SRC No. L1342-05

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Prepared for:

Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

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Virginia 22151

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EXECUTIVE SUMMARY

Information has been reviewed on ethylene oxide, propylene oxide, butylene oxide, and diepoxybutane. Annual production for 1978 was estimated at 5,012 million pounds, 2,047 million pounds, 5-7 million pounds, and <1,000 pounds, respectively. Ethylene oxide is primarily consumed as feedstock for ethylene glycol, glycol ethers, polyols and polyol ethers, and ethanolamines. The propylene oxide consumption pattern is similar; it is feedstock for polyols used for polyurethane polymers, propylene glycol, non-urethane polyols, and polyol and glycol ethers. Butylene oxide is primarily consumed as a stabilizer for chlorinated solvents. Small amounts (<0.1 million pounds) of ethylene oxide and of propylene oxide are applied as sterilants or pesticides to commodities, pharmaceuticals, medical devices, tobacco, and other items. Although this use is only a small fraction of the total epoxide consumption, it represents a considerable potential for human exposure.

The epoxides are prepared by oxidation of the corresponding olefins. Ethylene oxide manufacture utilizes catalytic oxidation of ethylene, while propylene oxide currently utilizes chlorohydrination or peroxidation.

No quantitative information was available on environmental release of the manufactured epoxides. Release factors are definitely low, but since annual epoxide manufacturing volume is so large, release of even a small fraction of the total could result in several hundred thousand pounds of emissions. Release could arise through fugitive emissions, venting losses, losses during handling, and release with waste streams. Application of epoxide as a sterilant or a pesticide places the user of the treated product at risk of exposure.

Epoxides are inadvertent products of combustion. They have been observed in emissions from fuel burning, in automotive exhaust, and in cigarette smoke. Also, alkanes can react by several atmospheric routes to yield epoxides.

The epoxides are mobile in the environment, but degrade by chemical and biochemical routes. In water they are subject to hydrolysis and reactions with anions such as chloride and bromide. At ambient temperature (25°C), maximum half-life is about two weeks. They degrade in soil by pathways similar to those in water. Epoxides will oxidize in the atmosphere. They appear about as reactive as acyclic and other cyclic ethers, which places them among the most reactive compounds. The epoxides applied as sterilants or pesticides are lost from the treated object by a combination of volatilization and degradation (with reaction pathways similar to those described for water). Although the epoxides are mobile (high vapor pressure and water solubility), the information on hand did not characterize transport between water and the atmosphere. The epoxides will not bioaccumulate.

The epoxides have produced varied toxic effects in man following acute inhalation or dermal exposure. These effects have involved the central nervous system, gastrointestinal tract, lungs, skin, and bone marrow. Dermal exposure to ethylene oxide has resulted in formation of large blisters. Clinical reports of reactions following intravenous use of ethylene oxide-sterilized medical devices show that hemolysis, anaphylactic reactions, and sensitization to the compound may be produced if sterilized plastic devices have been poorly aerated before use. Conjunctivitis and corneal burns have been seen following exposure to high levels of ethylene oxide and propylene oxide vapor. Diepoxybutane is the most acutely toxic agent of the group, showing lethal toxicity (i.p.) in experimental animals at levels of 16 mg/kg; ethylene oxide produces similar effects at levels approximately tenfold higher.

Metabolism of the epoxides is rapid, with most of the administered compound being removed by urinary excretion. Distribution throughout the body is widespread, although localization in certain tissues occurs.

Long-term exposure to the epoxides in worker populations has produced effects on the bone marrow, reproductive system, central nervous system, and peripheral blood. Lower limb neuropathy seen in three ethylene oxide sterilizer operators was shown to be reversible. Leukemia and anisocytosis have been reported in workers at ethylene oxide facilities, but this represents a small number of cases (4) in two reports. A Russian report has indicated increased miscarriages and toxicosis in pregnant ethylene oxide workers; levels of exposure and quantitation were not available to assess the relevance of this study.

Animal studies on prolonged exposure to epoxides show similar types of toxic effects, including bone marrow effects, anemia, neurotoxicity, and reproductive effects. There is therefore a good possibility that epidemiological studies now underway will confirm the preliminary reports made on some of these long-term human effects.

The epoxides have demonstrated mutagenic activity in a wide variety of systems. These include the Ames test, mutation of several plant species, various microbial system mutations, Drosophila lethal mutations, and mammalian genetic damage. This last system involves an increased production of chromosome breaks in mice and rats exposed to ethylene oxide or diepoxybutane. Diepoxybutane is the most effective mutagen of the group, due to its bifunctional reactive character, and acts as a direct mutagen. Ethylene oxide, propylene oxide, and butylene oxide also act directly in decreasing order of reactivity. However, ethylene oxide, unlike diepoxybutane, shows increased activity in the Ames test after microsomal enzyme activation, indicating that a more mutagenic product may be produced by this process.

Teratogenic effects have been observed following intravenous injection of pregnant rats with relatively large doses of ethylene oxide. Chloroethanol, a potential reaction product of ethylene oxide, has produced teratogenic effects in the chick embryo, but not in the CD-1 mouse.

Studies on the carcinogenic potential of the epoxides have produced varied results. Diepoxybutane has been studied most extensively and has been shown to induce tumors following skin painting and injection. This compound has also acted as a tumor initiating agent when applied to mouse skin before administration of a promoting agent. One report concerning germ-free mice raised on ethylene oxide-sterilized bedding showed numerous tumors in these animals. However, this was a retrospective observation and the causative agent was not characterized. Other studies with ethylene oxide administered by skin painting or injection have failed to show increased tumor production. Propylene oxide injected into rats has reportedly produced tumors; this is an early study which has not been confirmed. Skin painting with butylene oxide has shown no tumorigenic effects.

The long-term effects of these epoxides in human populations have not been extensively investigated. Based on the results of animal studies and preliminary reports from human studies, the epoxides produce effects involving the central nervous system, bone marrow, peripheral blood, and reproductive system. The incidence and reversibility of these effects are unknown at present. In addition, the carcinogenic and teratogenic activity of all of these compounds, although suspect, awaits confirmation.

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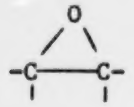
I. PHYSICAL AND CHEMICAL DATA

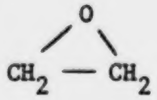
A. Structure and Properties

1. Chemical Structure and Nomenclature

Epoxides contain the three-membered cyclic ether structure depicted:



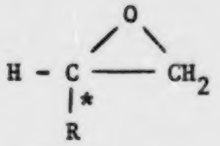
Nomenclature in Chemical Abstracts (CA) (or the International Union of Pure and Applied Chemists system) is based upon the simplest epoxide, oxirane, as a unique ring:



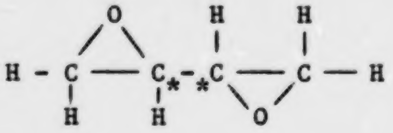
CA and IUPAC name all epoxides as derivatives of oxirane and apply the systematic nomenclature to ring substitution. Epoxides have several common nomenclature systems and they are usually discussed in the literature by common system names rather than by the IUPAC system names. The simple epoxides are most commonly named as olefin oxides (e.g., ethylene oxide) or as epoxyalkanes (e.g., epoxyethane).

This report reviews four epoxides and uses the names which are most generally applied to the selected epoxides: ethylene oxide; propylene oxide; butylene oxide; and diepoxybutane.

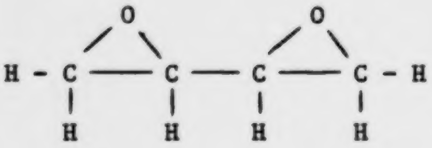
Three of the selected epoxides have asymmetric carbon atoms. Two of these, propylene oxide and butylene oxide, have a single asymmetric carbon:



This asymmetry results in optical activity, but does not otherwise affect physical or most chemical behavior (March, 1977; Lapkin, 1965). Since diepoxybutane has two asymmetric carbons, it exists as two distinct stereoisomers: an optically active form (the d,l pair):



and an optically inactive, meso form:



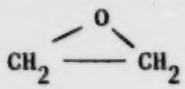
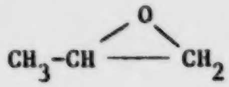
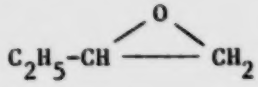
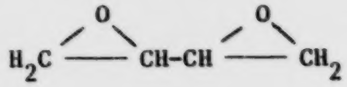
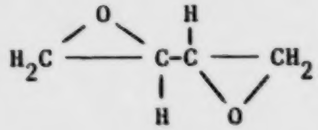
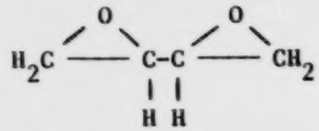
The physical and chemical properties of the two forms of diepoxybutane (d,l pair and meso form) are different.

Table 1 lists the structure, IUPAC names, common names and CAS Numbers of the selected epoxides.

2. Physical Properties of the Pure Material

Table 2 summarizes physical properties of the four epoxides selected for study. The epoxides are a class of ethers. The physical properties of the ethers have been associated with the net dipole moment of the

Table 1. Epoxide Structure and Nomenclature

Compound	CAS Number	IUPAC Name	Common Names
	75-21-8	Oxirane	Ethylene oxide[a,b,c]; dihydrooxirene, dimethylene oxide; 1,2-epoxyethane; oxacyclopropane; ETO; oxane; oxidoethane; α,β-oxidoethane
	75-56-9	Methyloxirane	Propylene oxide[b,c]; 1,2-epoxypropane[a]; methyl ethylene oxide; methyl oxirane; propene oxide
	106-88-7	Ethyloxirane	Butylene oxide; 1,2-epoxybutane[a]; butene oxide; ethyl ethylene oxide
	1464-53-5	2,2'-Bioxirane	Diepoxybutane[b]; 1,2,3,4-diepoxybutane; butadiene diepoxide; butadiene dioxide; 2,4-diepoxybutane; dioxybutadiene; erythritol anhydride
	298-180	(R*,R*)-(+ -)-2,2'-Bioxirane	D,L-diepoxybutane; 1,2,3,4-dianhydro-DL-threitol
	30419-67-1	[R-(R*,R*)]-2,2'-Bioxirane	D-diepoxybutane; 1,2,3,4-dianhydro-D-threitol; (2R,3R)-diepoxybutane
	30031-64-2	[S-(R*,R*)]-2,2-Bioxirane	L-diepoxybutane; 1,2,3,4-dianhydro-L-threitol; (2S,3S)-diepoxybutane
	564-00-1	(R*,S*)-2,2'-Bioxirane	Meso-diepoxybutane; 1,2,3,4-dianhydroerythritol; (R*,S*)-diepoxybutane

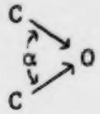
---

[a] Name listed in Registry of Toxic Substances (Fairchild *et al.*, 1977)
[b] Name listed in IARC (1976)
[c] DOT name

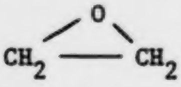
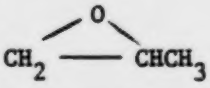
Table 2. Physical Properties of Epoxides. Adapted from BASF, 1972; Celanese Chemical Co., undated; Dow Chemical Co., 1977; Jefferson Chemical Co., undated a and b; Oxirane, undated; Union Carbide Corp., 1977; Weast *et al*., 1975; Gallant, 1967; Schultze, 1965; Gait, 1973; Lapkin, 1965.

	Ethylene Oxide	Propylene Oxide	Butylene Oxide	Diepoxybutane	
				d,l pair	meso
Molecular Weight	44.053	58.080	72.107	86.09	86.09
Index of refraction, n_D	1.3614 (4°C)	1.3632 (25°C)	1.381 (25°C)	1.4330 (20°C)	1.4330 (20°C)
Freezing point, °C	-112.44	-104;-112	-129.28	-16	4
Boiling point, °C at 760 torr	10.5	34.2	63.4	138 (767 torr)	144
Vapor pressure, torr at 25°C	1305	538	176		
Vapor density (air = 1.0)	149				
Specific gravity	0.8711_{20}^{20}	0.830_{20}^{20}	0.826_{25}^{25}	1.1157_{4}^{20}	1.13^{20}
Viscosity, cp	0.31 (4°C)	0.28 (25°C)	0.40 (25°C)		
Specific heat, cal/°C-g)	0.44 (20°C)	0.51 (20°C)			
Heat of vaporization (1 atm), cal/g	136.1	89			
Dipole moment, 10^{18} esu	1.9	1.88			
Flash point	<0°C	<-35°C			
Autoignition temperature in air, °F at 1 atm	804	869	822		
Flammability limits, Vol. %	3-100	1.8-36	1.9-19		
Critical Properties					
Temperature	195.8°C	209.1°C	243°C*		
Pressure	1043 psia	48.6 atm	630 psia*		
Density	0.315 g/ml*	0.312 g/ml	0.290 g/ml*		
Solubility, g/100g solvent					
Inorganic solvents (acetone, benzene, carbon tetrachloride, ether, methanol)	complete	complete	complete		
Epoxide in water	complete	59;66	9.5	miscible	soluble
Water in epoxide		15			

of the ether linkage (Morrison and Boyd, 1973). The normal ether linkage



has a C-O-C bond angle, α, of approximately 110°. The three-membered epoxide ring severely contracts this angle; α is 61° 24' in propylene oxide (Lapkin, 1965). The effect of the smaller angle of α on the physical properties of the epoxides appears consistent with an increase in polarity of the molecule. Epoxides exhibit higher melting points, boiling points, and water solubilities than ethers of similar chemical structure (Weast *et al*., 1975; Morrison and Boyd, 1973):

Molecule	Dipole Moment, 10^{18} esu	Molecular Weight	Melting Point, °C	Boiling Point, °C	Solubility
CH_3OCH_3	1.3	46	-140	-24	3700 cc/100g
	1.9	44	-111	11	complete
$CH_3OCH_2CH_3$	1.23	60		7	8 g/100g
	1.88	58	-112	34	59 g/100g

At ambient temperature ethylene oxide is a colorless gas with an ether-like odor. It condenses to a colorless liquid at 10°C. It is completely miscible with water and organic solvents. Ethylene oxide, like other epoxides, is hazardous to handle because of its high reactivity; the reactivity will be described in the section on chemical properties. It is extremely flammable from 3 to 100% by volume in air, explosive, and undergoes an exothermic, self-polymerization reaction (Dow Chemical Co., 1977; Jefferson Chemical Co., undated).

Properties of propylene oxide and butylene oxide are similar to ethylene oxide properties. All are members of the same homologous series and differ only by the number of methylene groups. Increasing the molecular weight in the series raises boiling and melting point, reduces water solubility, and reduces the flammability and explosion hazard.

Diepoxybutane does not belong to the same homologous series as the other three epoxides. As described in Section I.1, diepoxybutane occurs in two isomeric forms: meso, and the d,l-pair. Both forms have been prepared and some physical properties are available. Both forms have significantly higher melting points, boiling points and densities than butylene oxide.

3. Description of Grades of Material Available Commercially

With the possible exception of diepoxybutane the selected epoxides are refined to high purity for marketing; Tables 3, 4, and 5 describe the product specifications for commercial ethylene oxide, propylene oxide, and butylene oxide. No information was available on product specifications of diepoxybutane, which is only marketed in research quantities.

Commercial ethylene oxide has a purity greater than 99.9%. Specified impurities include trace quantities of water, aldehydes (specified as acetaldehyde), acid (specified as acetic acid), chloride, and an unspecified residue. Consideration of the ethylene oxide manufacturing process suggests the nature of potential impurities in the marketed product. Ethylene oxide can be prepared by two processes: via chlorohydrin or by direct oxidation

Table 3. Manufacturers' Specifications for Ethylene Oxide*

	BASF	Celanese	Dow	Jefferson	Shell	Wyandotte
Purity, wt. % min.	99.95	99.95				
Water, wt. % max.	0.005	0.02	0.03	0.03	0.03	
Aldehydes, as acetaldehyde, wt. % max.	0.005	0.01	0.005	0.025	0.010	0.003
Acidity as acetic acid, wt. % max.	0.002	0.002	0.002	0.005	0.0020	0.002
CO_2, wt. % max.	0.005		0.002			0.005
Total Cl as Cl^-, wt. % max.	0.005		0.005	nil		0.0005
Nonvolatile residue, gm/100 ml, max.	0.010	0.01	0.01**	0.01	0.010	0.01
Color, APHA, max.	10	10	5		10	10
Residual Odor		none		none	none	mild
Appearance		clear		clear	clear	
Acetylene, max.			0.0005	nil		

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*This information was obtained from the respective manufacturers product data sheets, available from each manufacturer on request.

**Presently 0.005 gm/100 ml in Dow ethylene oxide - Kurginski, Dow Chemical Co.

Table 4. Manufacturers' Specifications for Propylene Oxide*

	Dow	Jefferson	Oxirane
Specific Gravity	0.825-0.827 @25/25°C	0.829-0.831 @20/20°C	0.829-0.831 @20/20°C
Acidity as acetic acid, max.	20 ppm	0.005 wt. %	0.005 wt. %
Water, max.	500 ppm	0.050 wt. %	0.050 wt. %
Chloride ion, max.	40 ppm		0.010 wt. %
Color, APHA, max.	5	10	10
Aldehydes, total, max.	100 ppm	0.040 wt. %	0.040 wt. %
Appearance		clear	clear

*This information was obtained from product data sheets supplied by the manufacturers.

Table 5. Manufacturer's Specifications for Butylene Oxide (Dow Chemical Co., 1977)

Assay, (IR), min.	99.0%
Chloride ion, max.	0.05%
Aldehydes as butyraldehyde, max.	0.05%
Acidity as butyric acid, max.	0.01%
Water, max.	0.10%
Isobutylene oxide (IR), max.	0.30%
Color, APHA, max.	10

(see Section II.A.3). Chlorinated products from intermediate ethylene chlorohydrin can potentially remain as residues in refined ethylene oxide; the principle chlorinated organic products are 1,2-dichloroethane and bis(2-chloroethyl) ether (Schultze, 1965). Other potential by-products from the chlorohydrin process include inorganic chlorides, oxidation products (aldehydes, acids, etc.), hydrolysis products (glycol), and polymerized ethylene oxide. The most probable contaminants in ethylene oxide prepared by direct oxidation include oxidation products, hydrolysis products, ethylene oxide polymerization products, solvents, and traces of inorganic catalyst.

Propylene oxide is also manufactured via direct oxidation and chlorohydrin route (see Section II.A.3). The side reactions and by-products are expected to parallel those described for ethylene oxide (Lapkin, 1965; Gait, 1973).

Butylene oxide is prepared commercially by chlorohydrin technology (see Section II.A.3). The manufacturers' specifications describe the commercial product as 99.0% butylene oxide. The major contaminant is isobutylene oxide (0.3%), which is produced from isobutylene in the feedstock. Other contaminants are water, acid components (specified as butyric acid), aldehyde (specified as butyraldehyde), and chloride ion.

Diepoxybutane is manufactured in small quantities. No information was available on either the product specifications or potential contaminants in the product. Several routes are available for its preparation (see Section II.A.3) and the potential contaminants will depend, in part, upon the method used. Its preparation via 1,4-dichloro-2,3-dihydroxybutane will yield potential contaminants analogous to those in ethylene oxide prepared from ethylene chlorohydrin; potential contaminants would include chlorinated butanes, chlorinated butyl ethers, acids, aldehydes and ketones, chloride ion, water, alcohols, and products of self-condensation. Its preparation by the oxidation of butadiene with peroxides can be expected to yield similar by-products except for the chlorinated organics. Additional impurities could result from the feedstock, but lack of information about the latter precludes specific identification.

4. Physical Properties of Commercial Material

Since commercial grade ethylene oxide, propylene oxide, and butylene oxide are virtually pure materials, their physical properties are the same as those previously described for pure materials. No information was available on the physical properties of commercial diepoxybutane.

5. Description of Other Products of Which Epoxides May be a Contaminant

There was sparse information available in the literature on inadvertent epoxide production in other chemical processes. Inadvertent production is possible as the result of cyclization of glycols, olefin halohydrins, and similar products, which are usually either prepared from epoxides (see Section II.B.1) or epoxide precursors (Lande et al., 1979). The epoxides could also inadvertently form during alkane oxidation. Hayes (1963) mentions epoxides as trace by-products of saturated alkane oxidation in acetaldehyde manufacture. Schneider (1974) has a patented process for isoprene production from isobutane which yielded propylene oxide as a commercially important by-product. The process consisted of catalytic oxidation of isobutane with hydroperoxides. Although epoxides are potential by-products of alkane oxidation, no specific information was available on any commercial product contamination by any of the selected epoxides. Lowenheim and Moran (1975) described the butane oxidation process for acetaldehyde and did not include epoxides among the by-products. Pervier and coworkers (1974) have investigated some other processes which conceivably could yield epoxides, among which were ethylene oxidation to acetaldehyde; acetic acid production by butane oxidation; and ethyl acetate from oxidation of an acetic acid-ethylene mixture. While epoxides are likely products of side reactions, they are also likely to react. For example, glycols are observed by-products of alkane oxidation (Lowenheim and Moran, 1975), and from ethyl acetate manufacture (Pervier *et al*., 1974), and possibly are products of epoxide hydrolysis. In conclusion, epoxides are unlikely inadvertent contaminants of other manufactured products.

II. ENVIRONMENTAL EXPOSURE FACTORS

A. Production Aspects

1. Quantity Produced and Imported

a) Butylene Oxide

Commercial quantities of butylene oxide are produced by only one manufacturer in the United States; therefore, production quantities are not listed by the U.S. International Trade Commission. However, Cosslett and Gerry (1976) estimated that approximately 7 million lbs of n-butene were used in the synthesis of butylene oxide in 1974; this would correspond to a butylene oxide production of roughly 9 million pounds. Likewise, in 1977 an estimated 6.2 million pounds of butene were used to make butylene oxide (Hoff et al., 1978), which would correspond to an approximate production of 8 million pounds. Kurginski (1979) indicated that Dow Chemical believed that the U.S. production of butylene oxide in 1977 was 5.7 million pounds. According to these estimates, butylene oxide accounts for less than 0.1% of all epoxides produced domestically. Butylene oxide imports are considered negligible to nonexistent.

b) Ethylene Oxide

The quantities of ethylene oxide produced in the United States over the period 1970-1978 are summarized in Table 6. Ethylene oxide accounts for about 70% of the total annual epoxide production volume in the United States.

Imports of ethylene oxide, in million of lbs, are listed below (Blackford, 1976a):

1975	4.00
1974	1.51
1973	2.86
1972	7.21
1971	0.06

In 1978, 76 million pounds of ethylene oxide were exported (Anon., 1979a).

Table 6. Production Volumes of Ethylene Oxide and Propylene Oxide 1970-1978 (USITC, Annual)

Year	Quantities (Millions of Pounds)	
	Ethylene Oxide	Propylene Oxide
1978	5,012	2,047
1977	4,364	1,866
1976	4,184	1,823
1975	4,467	1,524
1974	4,200*	1,756
1973	4,167	1,753
1972	3,962	1,520
1971	3,598	1,194
1970	3,865	1,179

*revised figure

c) Propylene Oxide

The quantities of propylene oxide produced in the United States over the period 1970-1978 are indicated in Table 6. Propylene oxide accounts for about 30% of the total annual epoxide production volume in the United States.

Recent imports of propylene oxide, in millions of lbs, are listed below (Blackford, 1976b):

1975	20.99
1974	32.30
1976	33.07
1972	30.33
1971	33.34

Most imports of propylene oxide come from Canada; they amount to only 1-2% of the U.S. production. In 1978, 75 million lbs of propylene oxide were exported (Anon., 1979a). For 1979, export of propylene oxide was expected to rise above 100 million lbs with imports in the neighborhood of 100 million lbs (Anon., 1979b).

d) 1,2,3,4-Diepoxybutane

There is no evidence in the literature which indicates that 1,2,3,4-diepoxybutane is produced in commercial quantities. Therefore, it may be assumed that less than 1000 lbs per year are produced. Production appears limited to laboratory reagent supplies.

2. Producers, Production Sites, Production Capacity, Distributors, and Importers

a) Butylene Oxide

The only commercial producer of butylene oxide in the United States is Dow Chemical U.S.A. in Midland, Michigan. Production capacity was not available. The following companies can supply laboratory amounts of 2,3-butylene oxide (OPD Chemical Buyers Directory, 1977; Chemical Week, 1977):

Farchan Div., Chemical Samples Co.
Willoughby, Ohio

Research Organic/Inorganic Chemical Corp.
Sun Valley, Calif.

b) Ethylene Oxide

Table 7 lists the manufacturers who produce ethylene oxide and the plant locations. With a few exceptions, production is concentrated in the major industrial chemical centers of Texas and Louisiana. The total capacity of the United States to produce ethylene oxide is 5,931 million lbs annually (Chemical Profiles, 1978).

The manufacturers of ethylene oxide are the major users and distributors of the compound. Additional distributors of ethylene oxide include the following (OPD Chemical Buyers Directory, 1977; Chemical Week, 1977):

Air Products and Chems.	Allentown, Pa.
Arc Chem. Corp.	Slate Hill, N.Y.
Devon Chem. Inc.	Princetown, N.J.
MG Scientific Gases	Somerville, N.J.
Nippon Soda Co. Ltd.	Tokyo, Jap.
Scientific Gases	Plainfield, N.J.
Warren Chemical Co.	Seabrook, Md.

c) Propylene Oxide

Manufacturers producing propylene oxide and plant sites are listed in Table 8. As with ethylene oxide, a large percentage of the production capacity is located in the Texas and Louisiana area. The total capacity of the United States to produce propylene oxide is 2,944 million lbs annually (Chemical Profiles, 1979). By 1980, capacity may be up to 3,315 million lbs (Blackford, 1976b).

Table 7. Plant Capacity, Sites, and Manufacturers of Ethylene Oxide (Chemical Profiles, 1978; SRI, 1979; Kurginski, 1979)

Ethylene oxide (Dihydro-oxirene) (Dimethylene oxide) (1,2-Epoxy-ethane) (ETO) (Oxirane)		Annual Capacity (Millions of Pounds)
BASF Wyandotte Corp.	Geismar, La.	316
Calcasieu Chem. Corp.	Lake Charles, La.	225*
Celanese Corp.	Clear Lake, Tex.	475
Dow Chem., U.S.A.	Freeport, Tex.	260
	Plaquemine, La.	450
Eastman Kodak Co.	Longview, Tex.	195
Northern Petrochemical	Morris, Ill.	230
Olin Corp.	Brandenburg, Ky.	110
PPG Industries, Inc.	Beaumont, Tex.	155
	Guayanilla, P.R.	300
Shell Chem. Co.	Geismar, La.	670
SunOlin Chem. Co.	Claymont, Del.	100
Texaco Inc. Jefferson Chem. Co. Inc., subsid.	Port Neches, Tex.	675
Union Carbide Corp.	Seadrift, Tex.	850
	Taft, La.	1,100
	Penuelas, P.R.	550
	TOTAL	6,661

Note: Oxirane Chemical Co. which produces ethylene glycol directly from ethylene is given an oxide equivalent of 575 million pounds.

*Closed by fire and explosion, scheduled to reopen in 1980.

Table 8. Plant Capacity, Sites, and Manufacturers of Propylene Oxide (Chemical Profiles, 1979; SRI, 1979)

Propylene Oxide (1,2-Epoxypropane)		Annual Capacity (Millions of Pounds)
BASF Wyandotte Corp.	Wyandotte, Mich.	194
Dow Chem. U.S.A.	Freeport, Tex.	1100
	Plaquemine, La.	440
Olin Corp.	Brandenburg, Ky.	130
Oxirane Corp.	Bayport, Tex.	920
	Channelview, Tex.	400
	TOTAL	3,184

Dow Chemical Co. has the capability to switch some 200 million to 300 million pounds per year of propylene oxide capacity to ethylene oxide.

Jefferson Chemical Co., Inc., a subsidiary of Texaco, stopped producing propylene oxide December 1, 1978, but remains a merchant marketer of propylene oxide and derivatives through a tolling agreement with Oxirane Corp.

The manufacturers of propylene oxide are the major distributors of the compound. Additional distributors of propylene oxide include the following (Chemical Week, 1977):

Ashland Chemical Co.	Columbus, Ohio
McKesson Chemical Co.	San Francisco, Calif.

d) 1,2,3,4-Diepoxybutane

There are no known commercial producers of 1,2,3,4-diepoxybutane. Laboratory reagent quantities of the compound can be supplied by:

Pfaltz & Bauer	Stamford, Conn.
Matheson Coleman & Bell	Norwood, Ohio
Koppers Co.	Pittsburgh, Pa.

3. Production Methods and Processes

a) Butylene Oxide

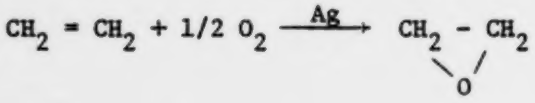
Butylene oxide is commercially prepared from 1-butene (Cosslett and Gerry, 1976). It is manufactured by Dow by utilizing chlorohydrin technology (Huff et al, 1978). The chlorohydrin process is described in the following ethylene oxide section.

b) Ethylene Oxide

Two major processes have been used to manufacture ethylene oxide in large, commercial quantities: the direct oxidation of ethylene and the chlorohydrination of ethylene.

In 1975, about 99% of all ethylene oxide was produced by the direct oxidation method (Blackford, 1976a). In this method, ethylene is oxidized in the vapor phase using either air or oxygen and a silver catalyst. Approximately 65% of industry capacity is based upon air and the remainder uses oxygen. There is a trend toward oxygen to increase yields (Blackford, 1976a).

The overall reaction may be represented as follows:



$$CH_2 = CH_2 + 1/2\ O_2 \xrightarrow{Ag} \underset{O}{CH_2 - CH_2}$$

One of the by-products of ethylene oxidation is ethylene glycol (Blackford, 1976a). This compound is often not considered a serious impurity because many of the ethylene oxide manufacturers use the oxide to produce this glycol. Some carbon dioxide and water are also formed by complete oxidation of ethylene (Lowenheim and Moran, 1975).

Figure 1 diagrams the process flow for production of ethylene oxide via oxidation. Ethylene (95-98% purity) and air are mixed in a volume ratio of 1:8 and passed over a catalyst of silver oxide deposited on an inert carrier. The catalyst is usually replaced every 18 months. Generally, an anticatalyst such as ethylene dichloride is added to the ethylene feed to suppress CO_2 formation. With process conditions consisting of atmospheric pressure and a temperature of 270-290°C, a reactor contact time of one second converts about 60% of the ethylene to the oxide. The effluent gases from the reactor are washed

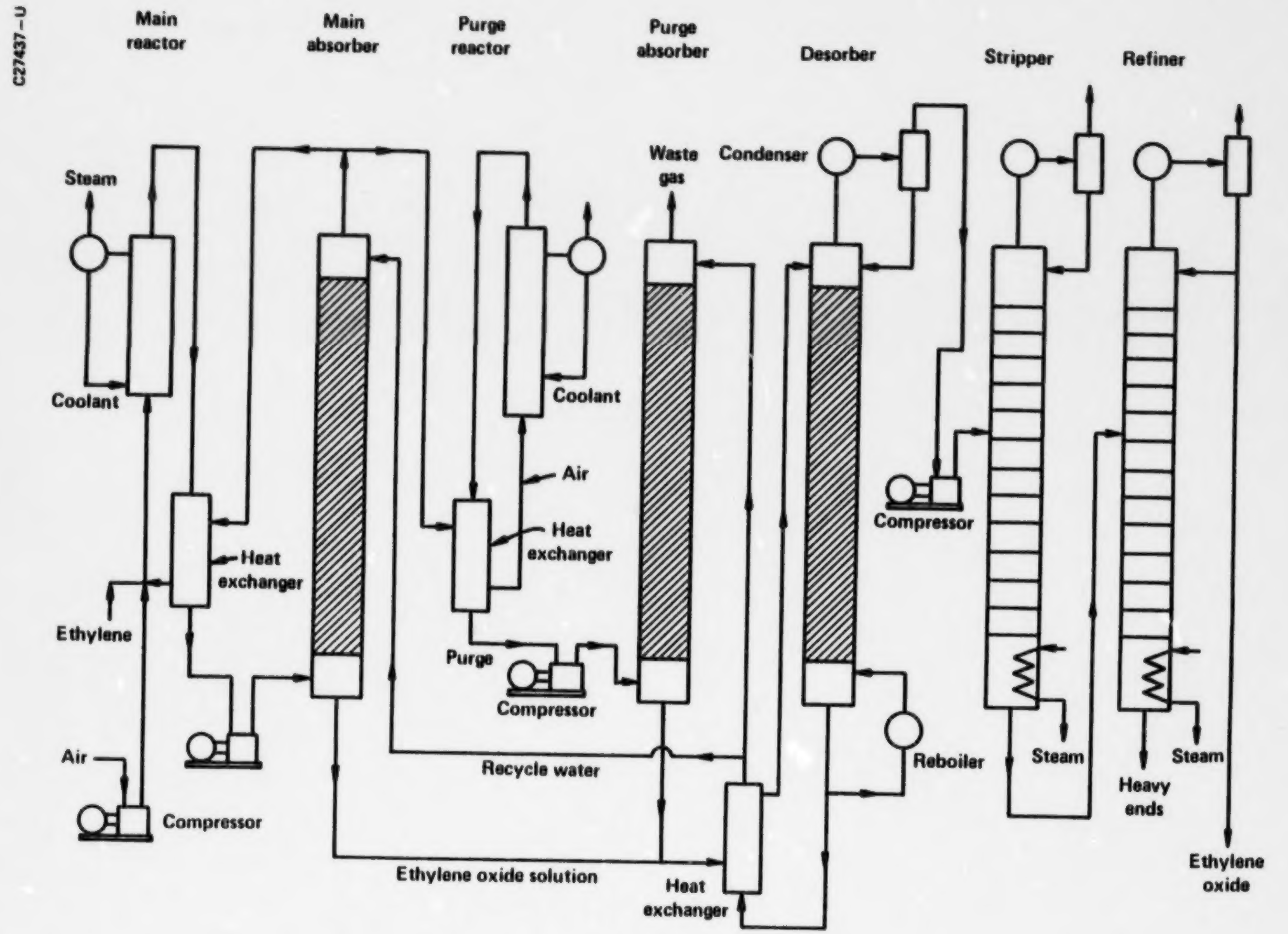


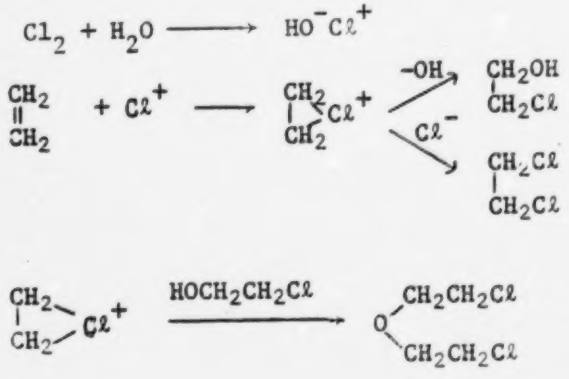
Figure 1. Direct-oxidation process for manufacturing ethylene oxide (Schultze, 1965).

with water under pressure in an absorber. The aqueous ethylene oxide solution is sent to a vacuum stripping column where ethylene oxide is liberated from solution and passed overhead to a fractionating column for final purification (Lowenheim and Moran, 1975).

Reactor design and process operations are not standardized throughout the ethylene oxide oxidation industry, so variations of the described process are in use (Lowenheim and Moran, 1975). The average industry yield of ethylene oxide from ethylene is about 64% of theoretical (Blackford, 1976a).

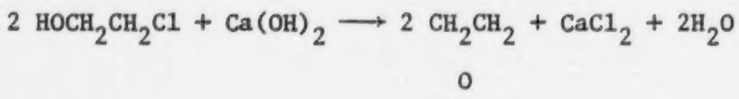
The chlorohydrin process was the main method of ethylene oxide manufacture until 1957. In 1972, the Dow Chemical Company converted the remaining chlorohydrin capacity to the production of propylene oxide, and the process was not used again for ethylene oxide production until 1975. The Dow Chemical Company has built-in flexibility for using the chlorohydrin process to produce either propylene oxide or ethylene oxide. Since 1975, part of this capacity has been used for ethylene oxide. During 1975, the Dow Chemical Company made between 25 to 50 million lbs of ethylene oxide via the chlorohydrin process (Blackford, 1976a), representing about 1% of the total U.S. production. The chlorohydrin process is attractive commercially only when a good supply of captive low-cost chlorine and lime or caustic soda is available. Also, satisfactory markets or disposal facilities are needed for the by-products produced (Schultze, 1965).

The chlorohydrin process starts by converting ethylene to ethylene chlorohydrin with hypochlorous acid. The chlorohydrin is converted to ethylene oxide by dehydrochlorination with slaked lime. The hypochlorous acid can be formed to two ways: (1) by mixing a slurry of hydrated lime with a stream of chlorine gas to yield the unstable calcium oxychloride which decomposes to give calcium chloride and hypochlorous acid, or (2) by dissolving chlorine gas in water. The hypochlorous acid then is reacted with ethylene to yield a 35% to 40% solution of ethylene chlorohydrin. However, two major by-products, 1,2-dichloroethane and bis(2-chloroethyl)ether, are formed during the chlorohydrin formation as shown:



From the equations above, it can be seen that the amount of 1,2-dichloroethane formed is dependent upon the ethylene and chlorine gas concentrations and that the amount of ether formed is dependent upon the ethylene chlorohydrin concentration. In most chlorohydrin processes, ether formation is minimized by avoiding high chlorohydrin concentrations (Lichtenwalter and Riesser, 1964).

The formation of ethylene oxide from ethylene chlorohydrin can be represented by the following equation:



$$2\ HOCH_2CH_2Cl + Ca(OH)_2 \longrightarrow 2\ \underset{O}{CH_2CH_2} + CaCl_2 + 2H_2O$$

A simplified diagram of a typical chlorohydrin process ethylene oxide plant is depicted in Figure 2. The reactor is usually a corrosion-resistant tower measuring 4 ft in diameter and 50 ft high. Its lower section contains spargers and porous plates for the effective dispersion of chlorine into water and for injecting ethylene into the hypochlorous acid medium. Ethylene chlorohydrin formation proceeds rapidly in the lower section of the tower. Gases are separated from the dilute chlorohydrin solution in the top section and the vent gases from the condensing apparatus pass in series to acidproof water and caustic scrubbers, where residual chlorine and HCl gas are removed before recycling the unreacted ethylene. The aqueous chlorohydrin solution is mixed with a 10% solution of milk of lime at the inlet to the hydrolyzer (Schultze, 1965).

The crude ethylene oxide product from the hydrolyzer contains about 77.5% ethylene oxide, 10% water, 12% chlorinated organic compounds (principally 1,2-dichloroethane and bis(2-chloroethyl)ether), and 0.5% acetaldehyde together with small amounts of hydrocarbon gases. This crude ethylene oxide is refined in two columns; the first column removes chlorinated hydrocarbons and the second removes acetaldehyde. Table 9 describes the quantities of reactants consumed and the products formed in the manufacture of 1000 lbs of ethylene oxide (80% yield).

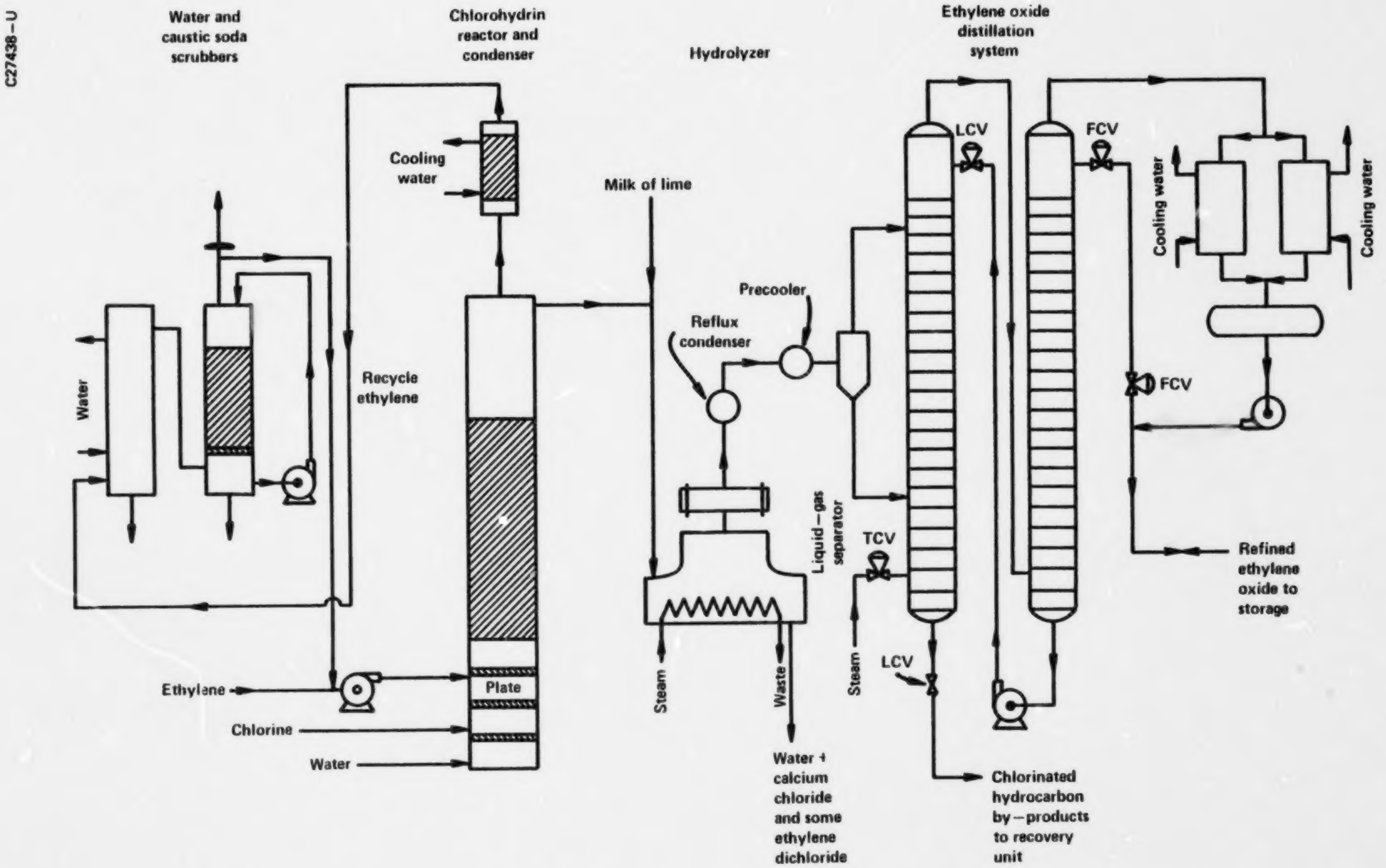

C27438-U
Water and caustic soda scrubbers
Chlorohydrin reactor and condenser
Hydrolyzer
Ethylene oxide distillation system
Cooling water
Milk of lime
Precooler
Reflux condenser
Recycle ethylene
Water
LCV
FCV
Cooling water
Cooling water
FCV
Liquid – gas separator
TCV
Refined ethylene oxide to storage
Ethylene
Plate
Chlorine
Water
Steam
Waste
Steam
LCV
Water + calcium chloride and some ethylene dichloride
Chlorinated hydrocarbon by – products to recovery unit

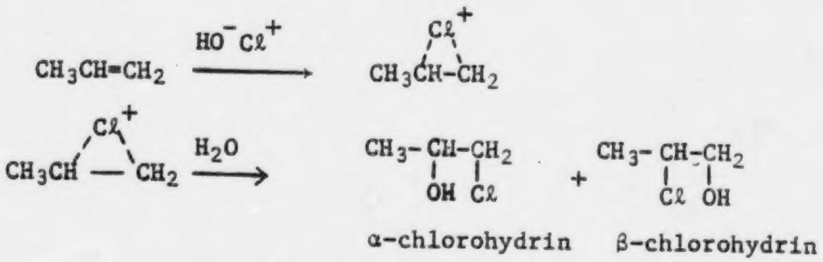
Figure 2. Chlorohydrin process for manufacturing ethylene oxide (Schultze, 1965).

c) Propylene Oxide

Two major processes are used to manufacture propylene oxide from propylene in large quantities: peroxidation and chlorohydrination. In 1978, about 41% of the total nameplate capacity for propylene oxide will be based on the peroxidation of propylene and the remainder on chlorohydrination (Blackford, 1976b).

The chlorohydrination processes for propylene oxide and ethylene oxide are related. The propylene oxide process yields a more complex mixture of by-products.

While propylene chlorohydrin, like ethylene chlorohydrins, is formed by reaction with hypochlorous acid, unlike the ethylene chlorohydrin process, two chlorohydrins are possible with propylene chlorohydrin and as a result three chloroethers may be formed:



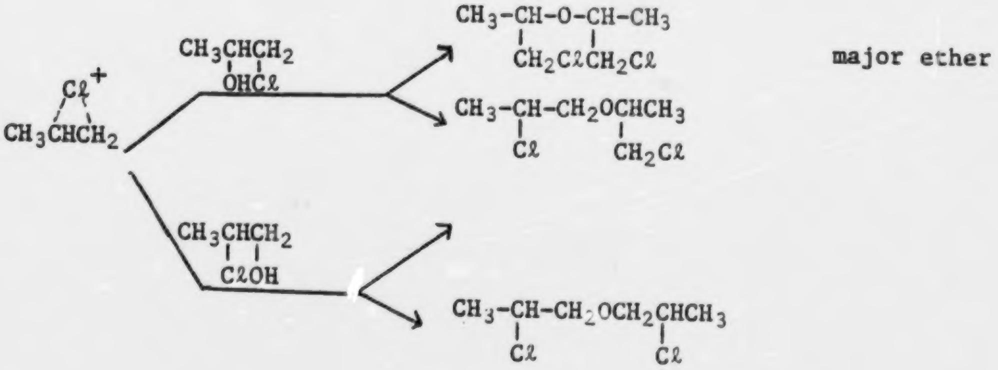
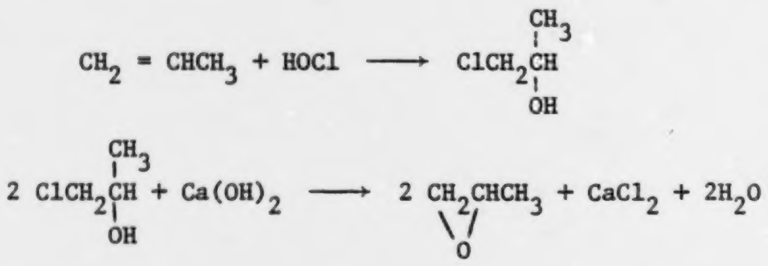


Table 9. Reactants and Products of the Ethylene Oxide Chlorohydrin Process (Schultze, 1965)

Reactants		Products	
Compound	Quantity (lbs)	Compound	Quantity (lbs)
Ethylene	800	Ethylene oxide	1000
Chlorine	2000	Calcium chloride	3200
Lime (as CaO)	1600	1,2-dichloroethane	100-150
		Bis(2-chloroethyl)ether	70-90
		Acetaldehyde	5-10

Although the α-chlorohydrin is the major product, because of the stability of the secondary carbon atom, some β-chlorohydrin forms, and the α-chlorohydrin: β-chlorohydrin isomer ratio varies from 3:1 to 9:1 depending on reaction conditions (Lapkin, 1965). The major by-product ether is bis(2-chloroisopropyl)ether. As with the production of ethylene chlorohydrin, a major by-product, which is formed in larger quantities than the ethers, is the propylene dichloride. A typical propylene chlorohydrin plant produces, for every 100 kg of propylene oxide, about 9 kg of propylene dichloride, 2 kg of dichloropropyl ethers, and 215 kg of calcium chloride brine (Lowenheim and Moran, 1975).

The overall reaction of the chlorohydrin process for production of propylene oxide can be represented by the following sequence:



$$CH_2 = CHCH_3 + HOCl \longrightarrow ClCH_2\underset{OH}{\overset{CH_3}{CH}}$$

$$2\ ClCH_2\underset{OH}{\overset{CH_3}{CH}} + Ca(OH)_2 \longrightarrow 2\ \underset{\diagdown O \diagup}{CH_2CHCH_3} + CaCl_2 + 2H_2O$$

A diagram of a typical chlorohydrin propylene oxide plant is depicted in Figure 3. Operation is similar to that of a chlorohydrin ethylene oxide plant. While yield varies from plant to plant, the industry average is estimated as 77% of theoretical propylene oxide from propylene (Blackford, 1976b).

The peroxidation of propylene to propylene oxide can be represented by the following reactions:

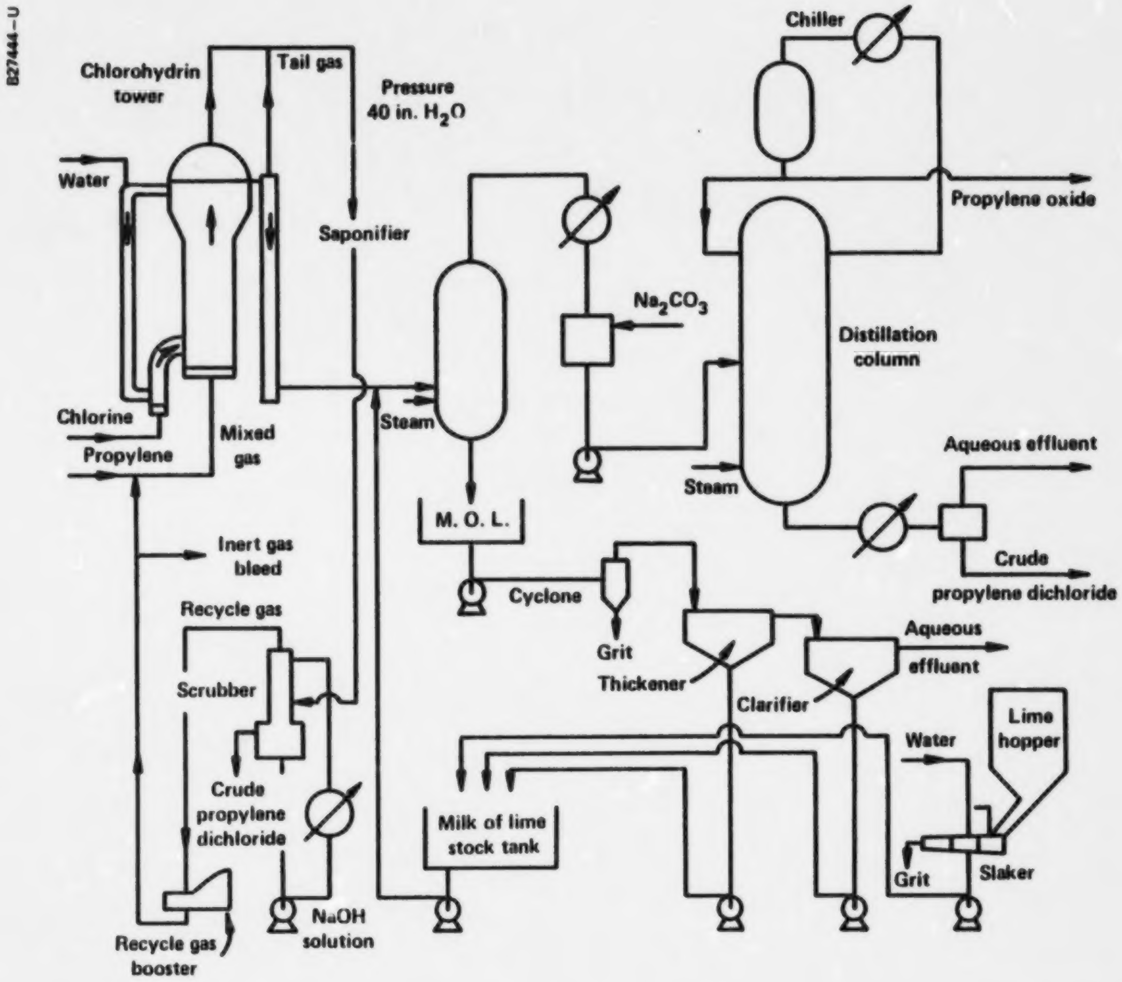
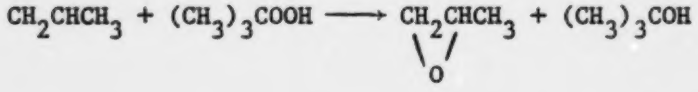


Figure 3. Diagram of a typical chlorohydrin propylene oxide plant (Fyvie, 1964).

$$2(CH_3)_3CH + 3/2\ O_2 \longrightarrow (CH_3)_3COOH + (CH_3)_3COH$$



$$CH_2CHCH_3 + (CH_3)_3COOH \longrightarrow \underset{\diagdown O \diagup}{CH_2CHCH_3} + (CH_3)_3COH$$

Propylene oxide is produced by a two-step process. Isobutane is air-oxidized in the liquid phase to tert-butyl hydroperoxide, which is used to oxidize propylene to the oxide. The diagram of this process is shown in Figure 4. The yield of propylene oxide is about 93% of theoretical using the peroxidation method; approximately 2.2 kg of tert-butyl alcohol are formed per kilogram of propylene oxide produced (Lowenheim and Moran, 1975). Feeds other than isobutane can be used. For example, in 1977, Oxirane Corporation brought on-stream a 400 million lb-per-year propylene oxide plant in Texas which uses ethylbenzene feed instead of isobutane. In this process, ethylbenzene hydroperoxide is formed and reacted with propylene to make propylene oxide and methyl phenyl carbinol; the carbinol is used to make styrene (Soder, 1977). Because of the large amounts of coproducts formed, the economics of the peroxidation methods depend as much on the coproducts as on the propylene oxide market.

Several patents on propylene oxide production have been reported in the literature. These are new technologies which could impact on future production practices, but are not in use at the present time.

A new technology has been described for the chlorohydrin approach (Anon., 1978b,c). The technical advancement will alter the process by recycling the brine waste (Figure 5). This waste will be purified and sent to a chlorine-caustic cell. Chlorine will be reacted with t-butyl alcohol to yield t-butyl hypochlorite, which will be the chlorinating agent.

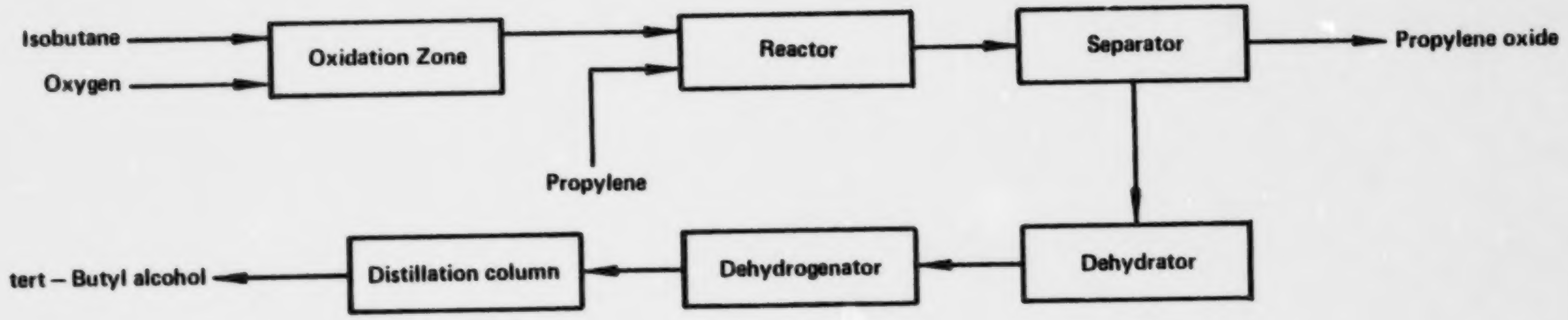


Figure 4. Preparation of propylene oxide by peroxidation of propylene (Lowenhiem and Moran, 1975).

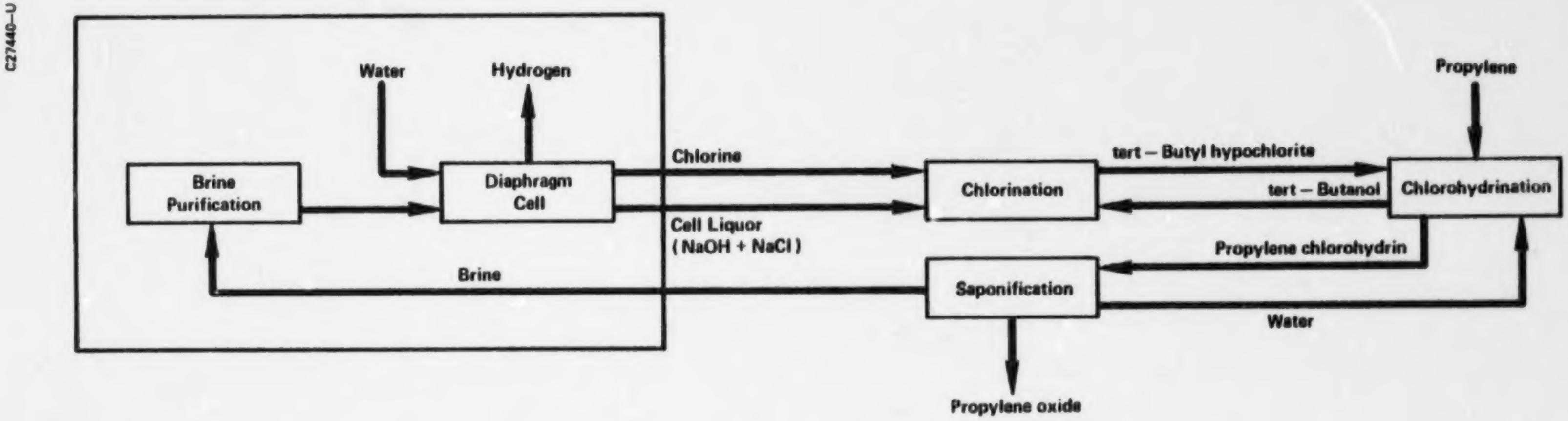


Figure 5. Chlorohydrin-propylene oxide production modified by electrolytic regeneration of chlorine (Anon., 1978b).

Adaptations of the peroxidation method would utilize new methods for peroxide generation and modify the reaction sequence (Anon., 1977c, 1978a,c,d; Rozenzweig, 1977). One approach employs as feed a mixture of propylene, oxygen, and acetic acid. The reaction sequence initiates with peracetic acid formation. The sequence continues with olefin epoxidation and conversion of the epoxide to propylene glycol monoacetate. Propylene oxide subsequently is prepared by cracking the glycol acetate. Another procedure utilizes a feed of propylene with an acetaldehyde-ethyl acetate mixture for peracetic acid preparation. The process, which also produces acetic acid, will require an acetic acid market. Other advancements in the hydroperoxide technology utilize transition metal (Mo, V, Cr, or W) or arsenic compounds as catalyst.

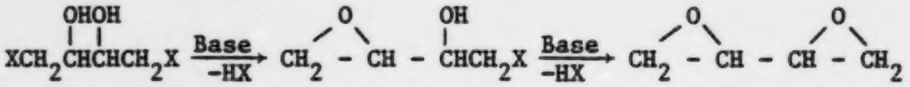
Perhaps the most important new technology would produce propylene oxide by direct, catalytic oxidation (Anon., 1977c). The patented procedure utilizes as catalyst an arsenical compound which contains polycyanoethylene ligands. Reaction conditions are 150°C and 850 psi with two-hour contact time. The procedure produces propylene oxide with 48% conversion and 52% efficiency.

d) Diepoxybutane

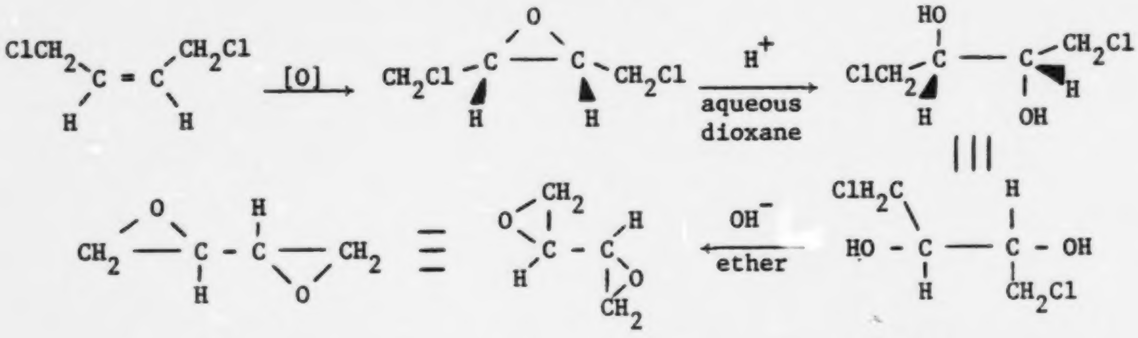
Domestic production of diepoxybutane appears limited to relatively small amounts for laboratory use or as a specialty chemical. The two diepoxybutane isomers (see Section I.A.1) have been prepared by a variety of synthesis schemes, which all involve alkaline-assisted cyclization of butanediol or butanetetraol derivatives.

Most of the synthetic schemes employ the S_Ni (internal nucleophilic substitution) cyclization of 1,4-dihalo-2,3-butanediols

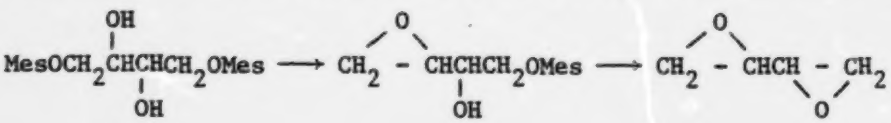
(Wallace, 1965; IARC, 1976). The dichloro- and dibromobutanediols have been utilized as precursors:



The S_Ni reaction is stereospecific; while *threo*-2,3-butanediol yields the *d,l* isomer, the *erythro*-2,3-butanediol is precursor for the *meso*-isomer. A method for preparing the isomeric epoxybutanes from 1,4-dichloro-2-butene has been developed (Starcher *et al.*, 1958; Benerito *et al.*, 1964). Preparation of the individual isomers is possible, since the isomeric diepoxybutanes can be individually prepared. While *trans*-1,4-dichloro-2-butene is a precursor for *meso*-diepoxybutane, *cis*-1,4-dichloro-2-butene is a precursor for *d,l*-diepoxybutane. The overall sequence for the *d,l* isomer is illustrated:



Feit and coworkers (1970) have prepared optically active, (2S,3S)-diepoxybutane by a slightly different syntheses. The precursor was the 1,4-bismethanesulfonate of (2S,3S)-threitol; the epoxidation was alkaline assisted, as discussed above for preparation from dichlorobutanediols:



4. Market Price and Influencing Factors

Current selling prices for bulk commercial quantities of the epoxides are listed in Table 10. Ethylene oxide, propylene oxide, and butylene oxide are bulk chemicals. Diepoxybutane is sold only in small quantities for laboratory and research purposes for a price ranging from $1.20-$1.95 per gram.

In the early 1970's, ethylene oxide was being sold for roughly seven cents per pound. However, ethylene oxide supplies became severly limited and the price for ethylene feedstock rose rapidly causing producers to successively raise prices to 26-28.5 cents per pound by April 1975 (Blackford, 1976a).

Similar factors, demand for propylene oxide and rising costs of propylene feedstock caused prices for propylene oxide to rise from 8.5 cents per pound in 1971 to 23-25 cents per pound in 1975 (Blackford, 1976b).

5. Market Trends and Influencing Factors

a) Butylene Oxide

Domestic production of butylene oxide in the near term is expected to decline; Cosslett and Gerry (1976) have estimated that the 1980 production of butylene oxide will total only 15% of the 1974 production. The main use of butylene oxide is to stabilize chlorinated solvents such as trichloroethylene and 1,1,1-trichloroethane. A projected decline in use of these chlorinated solvents appears to be part of the reason for the predicted decline in domestic butylene oxide production. Another reason for predicting a decline in domestic production is that the Dow Chemical Company's patents on butylene oxide production expire in 1979 making it feasible for the Showa Denko Chemical Company of Japan to build a butylene oxide facility with a 4.4 million lb/yr capacity (Anon., 1978d,f). Output from this competing facility could effectively reduce the Dow Chemical Company's overseas markets for butylene oxide.

Table 10. Domestic Prices for Various Epoxides*

Epoxide	Price	Reference
Butylene Oxide	\$1.65/lb (bulk)	Dow Chem. Sales Off., Buffalo, NY
Ethylene Oxide	\$0.36/lb (bulk)	Chem. Mktg. Rptr., Jan. 21. 1980
Propylene Oxide	\$0.25/lb (bulk)	Chem. Mktg. Rptr., Jan. 21, 1980.
1,2,3,4-Diepoxybutane	\$19.50/10 grams	Pfaltz & Bauer Catalog

*Note that prices of petrochemicals can change rapidly due to the energy crisis.

b) Ethylene Oxide

Figure 6 shows plant capacity and production data for ethylene oxide from 1950 to 1977. The growth in the consumption of ethylene oxide has largely depended upon its use as an intermediate for ethylene glycol production (Blackford, 1976a; Chemical Profiles, 1975a). Although future growth of ethylene glycol for use in polyesters is expected to be considerably less dramatic than it was during the recent past, ethylene glycol is estimated to grow in the range of 7% to 8% per year in the near future (Anon., 1977a).

If all of the announced expansions for ethylene oxide come on stream as scheduled, United States ethylene oxide capacity will increase to 6,400 million lbs annually in 1979 (Chemical Profiles, 1978). Provided there is sufficient ethylene feedstock available, consumption of ethylene oxide is expected to increase at an average rate of approximately 4.7% to 5.2% per year until 1980 (Blackford, 1976a). Chemical Profiles (1978) has projected a 5% annual growth rate for ethylene oxide until 1982. Ethylene feedstock is not expected to be in short supply through 1980, if all announced new plants and expansions come on stream as planned.

c) Propylene Oxide

Although propylene oxide production was down in recessionary 1975, its production rebounded strongly in 1976 and 1977. Future growth of the propylene oxide market depends upon its two major uses: propylene glycol and polypropylene glycol, and polyether polyols for urethanes. Various sectors of the urethane market are expected to grow from 8 to more than 10% annually; the overall growth rate of the propylene oxide market is expected

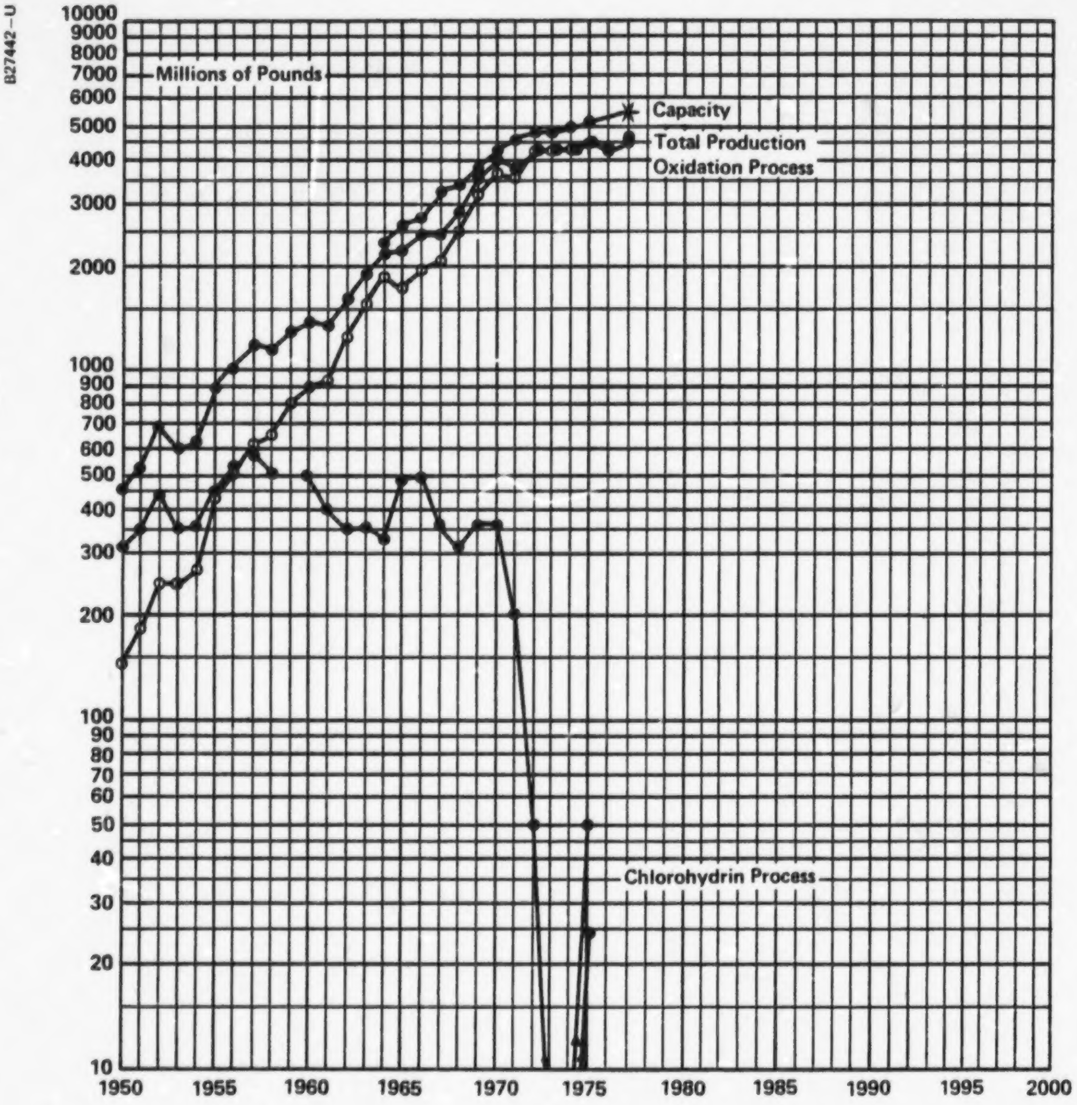


Figure 6. Market trends for ethylene oxide (Blackford, 1976b; SRI, 1977; USITC, Annual).

to increase about 5.5% to -6.0% per year through 1983 (Chemical Profiles, 1979). No significant new uses of propylene oxide are forecasted.

United States propylene oxide capacity is estimated at 2,944 million lbs per year for 1979/1980 (Chemical Profiles, 1979). The estimated demand for propylene oxide in 1983 is 2,691 million lbs (Chemical Profiles, 1979). Most industry estimates on propylene feedstock forecast a comfortable situation for users over the next few years (Anon., 1977b). Therefore, raw material supply should not be a limiting factor in the near future.

B. Use Aspects

1. Consumption by Major and Minor Use, Manufacturers and Use Sites

a) Butylene Oxide

Currently, more than 95% of the butylene oxide produced annually is used as a stabilizer in chlorinated solvents, such as 1,1,1-trichloroethane (methyl chloroform) and trichloroethylene (Taylor, 1978). Depending upon the solvent's use, up to 8% butylene oxide may be added to the chlorinated solvent but is usually closer to 0.7 wt %.

There are several minor uses of butylene oxide. For example, it is used to reduce corrosion in oil and gas well casings (Dow Chemical Co., 1977). Other current commercial applications include use in production of pharmaceuticals, surfactants, and agrachemicals (Anon., 1978d).

Exports of butylene oxide are not listed separately by the Department of Commerce (Bureau of the Census). However, it has been suggested that the Dow Chemical Company is currently enjoying a virtual world monopoly on 1,2-butylene oxide production due to patent restrictions which are due to expire in 1979 (Anon., 1978d). Under these circumstances, it seems likely that a sizeable portion of the Company's production is currently exported.

b) Ethylene Oxide

A description of the various uses of ethylene oxide is given below:

	Lawler, 1977	Chemical Profiles, 1978
Ethylene glycol	63%	60%
Nonionic surface-active agents	11%	11%
Glycol ethers	6%	
Diethylene glycol	5%	
Ethanolamines	5%	7%
Triethylene glycol	2%	
Polyethylene glycol	2%	Glycolethers 7%
Exports	2%	
Miscellaneous applications	4%	Other 16%

The major users and use sites for ethylene oxide are listed in Table 11; as can be seen from this table, a very large percentage of production is captively consumed by the primary manufacturers. A general description of the various uses of ethylene oxide is presented below.

Ethylene Glycol: By far, the largest single use of ethylene oxide is as an intermediate in the synthesis of ethylene glycol, which is currently produced by hydration of ethylene oxide. Current industry capacity to produce ethylene glycol is 5,155 million lbs annually (SRI, 1977). The growth in consumption of ethylene oxide has largely depended on its use as an intermediate for ethylene glycol production (Blackford, 1976a). Ethylene glycol is mainly used for polyester production and antifreeze formulations (Anon., 1977a; IARC, 1976).

Nonionic Surface-Active Agents: Approximately 25% of the nonionic surface-active agents synthesized from ethylene oxide are of the cyclic variety while 75% are of the acyclic variety. In the cyclic group, ethylene oxide is used to make ethoxylate alkyl phenols and alkylphenol-formaldehyde condensates. Production of ethoxylated nonylphenol is probably the largest volume product of the cyclic group; another large-volume product is ethoxylated dodecylphenol. Industry estimates of ethylene oxide consumption growth rates for cyclic surface-active agents range from -2% to +4% per year through 1980 (Blackford, 1976a). These surface-active agents are primarily used in detergents.

The acyclic surface-active category includes ethylene oxide used in the synthesis of surface-active polyethylene glycol esters,

Table 11. Users and Use Sites of Ethylene Oxide (SRI, 1977)

		Ethylene Glycol	Glycol Ethers	Diethylene Glycol	Ethanolamines	Triethylene Glycol	Polyethylene Glycol
BASF Wyandotte Corp.	Geismar, La.	X		X			
	Wyandotte, Mich.						X
Calcasieu Chem.	Lake Charles, La.	X					
Celanese Chem.	Clear Lake, Tex.	X		X		X	
Dow Chem.	Freeport, Tex.	X		X	X	X	X
	Plaquemine, La.	X		X		X	
	Midland, Mich.		X		X		
Eastman Kodak	Longview, Tex.	X	X	X		X	
Northern Petrochem.	Morris, Ill.	X		X			
Olin Corp.	Brandenburg, Ky.	X	X	X	X	X	X
PPG Ind.	Beaumont, Tex.	X	X	X		X	
	Guayanilla, PR	X		X		X	
Shell Chem.	Geismar, La.	X	X	X		X	
Texaco Jefferson Chem.	Port Neches, Tex.	X	X	X	X	X	X
Union Carbide	Seadrift, Tex.	X	X	X	X	X	
	Taft, La.	X	X	X		X	
	Penuelas, PR	X	X	X		X	
	Texas City, Tex.			X			
	Institute & S. Charleston, W. Va.						X
Ashland Chem.	Janesville, Wisc.						X
Hodag Chem.	Skokie, Ill.						X

ethoxylated alcohols, polyether polyols, ethoxylated fats and oils, and miscellaneous ethoxylated products, such as mercaptans, glycols, and polyols (Blackford, 1976a). Industry estimates that ethylene oxide consumption for acyclic surface-active agents is expected to increase at an annual rate of 8% to 9% through 1980. The manufacture of ethoxylated linear alcohols, used in heavy-duty liquid detergents, will account for most of this growth (Blackford, 1976a).

Di-, Tri-, and Polyethylene Glycols: Ethylene oxide and ethylene glycol react to form diethylene glycol, triethylene glycol, and polyethylene glycol. Diethylene and triethylene glycols are obtained mainly as by-products of ethylene glycol manufacture. Diethylene glycol is used to produce polyester resins, as a textile lubricant, and in solvent extraction. Triethylene glycol is used as a humectant and in natural gas dehydration, vinyl plasticizers, and polyesters. Industry capacity to make diethylene glycol is 472 million lbs per year; capacity to make triethylene glycol is about 145 million lbs per year (SRI, 1977).

Glycol Ethers: Ethylene oxide is combined with alcohols to manufacture glycol monoethers, which include ethylene glycol monomethyl, monoethyl and monobutyl ethers, diethylene and triethylene monoethyl, monomethyl, and monobutyl ethers. Ethylene oxide consumption for these ethers is expected to increase at an average rate of 6% per year to 1980 (Blackford, 1976a). Solvent applications dominate the many uses of glycol ethers. Industry capacity to make glycol ethers is 865 million lbs annually (SRI, 1977).

Ethanolamines: Ethylene oxide reacts with ammonia to form a mixture of mono-, di-, and triethanolamines. The proportion of the three ethanolamines is dependent upon the ratio of reactants used. Ethylene oxide consumption for ethanolamines is expected to increase at a rate of 8% to 12.8% annually to 1980 (Blackford, 1976a). About 25% to 30% of all ethanolamines are used for soaps and detergents, 5% to 20% for gas conditioning, 10% by the metal industry, 8% for textiles, 5% to 15% for toilet goods, and the remainder in varied applications (Blackford, 1976a). Industry capacity to make ethanolamines in 415 million lbs annually (SRI, 1977).

Miscellaneous Applications: Ethylene oxide is consumed in the synthesis of numerous commercial chemicals. The largest amount in the miscellaneous group goes into production of polyether polyols for flexible polyurethane foams. In 1975, about 75 million lbs of ethylene oxide were consumed in these polyols (Blackford, 1976a).

Approximately 13 to 18 million lbs of ethylene oxide are annually used to make the medicinals, choline and choline chloride (Blackford, 1976a).

As much as 20 million lbs of ethylene oxide were consumed in the production of ethylene chlorohydrin in 1974 by the Union Carbide Corporation for use as an intermediate in chemical synthesis (Blackford, 1976a). However, the Union Carbide Corporation is not currently making ethylene chlorohydrin.

Approximately 10 million lbs annually of ethylene oxide are used in the manufacture of hydroxyethyl starch which is a semi-synthetic gum used in textile sizing and adhesives (Blackford, 1976a). Hydroxyethyl cellulose is produced by reacting cellulose with ethylene oxide. In 1975, 20 million lbs of ethylene oxide were used to make these adhesive additives (Blackford, 1976a).

Arylethanolamines are made by reacting ethylene oxide with either aniline or aniline derivatives. It is estimated that 3 million lbs of ethylene oxide were used for arylethanolamines in 1974 (Blackford, 1976a). They are used as intermediates for monoazo dyestuffs.

Acetal copolymer resins are produced by catalytically copolymerizing 1,3,5-trioxane with a cyclic ether having at least two adjacent carbon atoms (e.g., ethylene oxide). Ethylene oxide consumption for these resins is believed to have amounted to about 2 to 3 million lbs per year from 1972 to 1975. Acetal copolymer resins are made by Celanese Plastics at Bishop, Texas under the trade name Celcon® (Blackford, 1976a).

Like nonionic surface-active agents, ethylene oxide is used to produce ethoxylated cationic surface-active agents. Several million lbs of ethylene oxide are annually used to produce these cationic agents such as ethoxylated (coconut oil alkyl) amine, ethoxylated (tallow alkyl) amine, and various ethoxylated fatty acid amino amides (Blackford, 1976a).

Small amounts of ethylene oxide are also consumed as a fumigant, as a food and cosmetic sterilant, and in hospital sterilization (Gilmour, 1978). In 1975, an estimated 0.1 million lbs of ethylene oxide were used for fumigant purposes (Landels, 1976). However, 1979 Dow Chemical (Kurginski, 1979) has estimated that 0.2% of production (∿10 million lbs/yr) of ethylene oxide is used as a fumigant.

c) Propylene Oxide

An analysis of the various uses of propylene oxide is given below (Lawler, 1977; Blackford, 1976b; SRC Estimates):

Polyurethane polyols	54.5%
Propylene glycol	19.5%
Non-urethane polyether polyols	6 %
Exports	6-7 %
Surface-active agents	4 %
Dipropylene glycol	2.5%
Glycerine	2 %
Glycol ethers	2 %
Miscellaneous	2.5-3.5%

The major users and use sites are described in Table 12. A general description of the various uses of propylene oxide is given below.

Polypropylene Polyols: Propylene ether polyols are consumed primarily for polyurethane polyols and in a minor amount for non-polyurethane applications. The polyols for polyurethane application are utilized in the production of flexible and rigid foam, which are used in furniture, automobile seating, insulation and packaging. Growth rate for propylene oxide in polyurethane polyols is forecast at 15% annually to 1980 (Blackford, 1976b).

The majority of the propylene oxide consumed as polyether polyols for non-urethane uses went into the production of random and block copolymers of polypropylene glycol and polyethylene glycol; the remainder was consumed in the production of polypropylene glycol for industrial purposes. Non-urethane markets for these compounds include surface-active agents, functional fluids, lubricants, and heat transfer fluids (Blackford, 1976b).

Propylene Glycol: While propylene glycol has many uses, production of polyester resins is the most important. Annual growth rate of propylene glycol is expected to average 7% to 8% per year to 1981 (Chemical Profiles, 1977a). Propylene glycol is made by companies producing propylene oxide. Industry capacity is 695 million lbs annually (SRI, 1977).

Surface-Active Agents: Propylene oxide is used in production of a wide variety of surface-active agents, among which are amphoteric surface-active agents, anionic agents, cationic agents, and nonionic agents. Most of these surface-active agents are some form of propoxylated compound. Mixed linear propoxylated alcohols have the largest production volumes. The largest market for the block copolymers surface-active agents is in crude-oil demulsifiers used in breaking water-in-oil emulsions (Blackford, 1976b).

Table 12. Users and Use Site of Propylene Oxide (SRI, 1977)

		Polypropylene Polyols for Urethane Application	Polypropylene Polyols for Non-urethane Application	Polypropylene Glycol	Surface Active Agents	Dipropylene Glycol	Propylene Glycol Ethers
Ashland Oil, Inc.	Janesville, Wisc.		X				
BASF Wyandotte Corp.	Geismar, La.	X					
	Washington, NJ	X	X				
	Wyandotte, Mich.	X	X				
Baychem Corp.	New Martinsville, W.Va.	X					
E.R. Carpenter Co.	Bayport, Tex.	X					
Dow Chemical	Midland, Mich.		X				X
	Freeport, Tex.	X	X	X		X	
	Plaquemine, Tex.			X		X	
ICI America	New Castle, Del.	X			X		
Jefferson Chemical Co.	Austin, Tex.	X				X	
	Conroe, Tex.	X					
	Port Neches, Tex.	X		X			
Olin Corp.	Lake Charles, La.	X					
	Brandenburg, Ky.	X	X	X		X	
Owens-Corning Fiberglass	Newark, N.J.	X					
Pelron Corp.	Lyons, Ill.	X					
PPG Indust.	Circleville, Oh.	X					
Union Carbide Corp.	Institute & South Charleston, W.Va.	X		X		X	X
	Seadrift, Tex.	X					
The Upjohn Corp.	LaPorte, Tex.	X					
Witco Chem. Corp.	Clearing, Ill.	X			X		
	Los Angeles, Ca.				X		
	Perth Amboy, N.J.				X		
Hoadag Chem. Corp.	Skokie, Ill.		X		X		
Nalco Chem. Corp.	Sugarland, Tex.		X				
Emery Indust.	SantaFeSprings, Ca.		X				
Magna Corp.	Houston, Tex.		X				
Petrolite Corp.	Brea, Ca.		X				
	St. Louis, Mo.		X				
Celanese Corp.	Bishop, Tex.			X			
Oxirane	Bayport, Tex.			X		X	

Table 12. Users and Use Site of Propylene Oxide (SRI, 1977)

		Polypropylene Polyols for Urethane Application	Polypropylene Polyols for Non-urethane Application	Polypropylene Glycol	Surface Active Agents	Dipropylene Glycol	Propylene Glycol Ethers
SCM	Chicago, Ill.				X		
Akzona, Inc.	McCook, Ill.				X		
The C.P. Hall Co.	Chicago, Ill.				X		
PVO Int'l.	Boonton, N.J.				X		
Dupont	Niagara Falls, N.Y.	X					
Minn. Mining & Mfg.	Decauter, Ala.	X					
Scher Bros., Inc.	Clifton, N.J.				X		
E.F. Hougton & Co.	Carrolton, Ga.				X		
	Philadelphia, Pa.				X		
Diamond Shamrock	Charlotte, N.C.				X		
Glyco Chems, Inc.	Williamsport, Pa.				X		
Andrew Jergens Co.	Cincinnati, Oh.				X		
Wilson Pharm. & Chemica Corp.	Philadelphia, Pa.				X		

Dipropylene glycol is primarily used to make polyester resins and plasticizers; growth rate is expected to average 8% per year to 1979 (Chemical Profiles, 1975b). Dipropylene glycol is produced by the producers of propylene oxide.

Glycerine: In 1975, FMC Corporation in Bayport, Texas, consumed roughly 26 million lbs of propylene oxide in the production of glycerine (Blackford, 1976b). Glycerine is mainly used as an ingredient in drugs and cosmetics, and in alkyd resins.

Glycol Ethers: Propylene oxide is combined with alcohols (methanol, ethanol, and isobutylalcohol) to manufacture glycol monoethers. The most important group of compounds is made from methanol. The reaction does not stop at the monoglycol ether, since some propylene oxide reacts with residual hydroxyl groups to form monoethers of di- and tripropylene oxide.

Propylene oxide consumption for glycol ethers is expected to increase annually about 8% to 1980 (Blackford, 1976b). Glycol ethers are useful as solvents in the coating industry and as lubricants and coupling agents.

Miscellaneous: Propylene oxide and ammonia react to form mono-, di-, and triethanolamines in a manner similar to the reaction of ethylene oxide and ammonia to form ethanolamines. These chemicals, isopropanolamines, are produced by the Dow Chemical Company in Midland, Michigan. It was estimated that in 1975, from 10 to 15 million lbs of propylene oxide were consumed in production of isopropanolamines (Blackford, 1976b). The latter are used to make isopropanolamides and isopropanolamine soaps.

Approximately 1 to 2 million lbs per year of propylene oxide are used to make propylene carbonate for solvent extractions, plasticizers, syntheses, and natural gas purification (Blackford, 1976b).

Propylene oxide has other minor applications in the production of hydroxypropyl cellulose, starch, and many miscellaneous chemicals. Hercules Incorporated makes a sulfur-vulcanizable elastomer from propylene oxide and allyl glycidyl ether called Parel®, which is used in automotive engine mounts. Propylene oxide is also used as a low-boiling solvent for nitro cellulose adhesives, as a fumigant, and as a food preservative (Blackford 1976b).

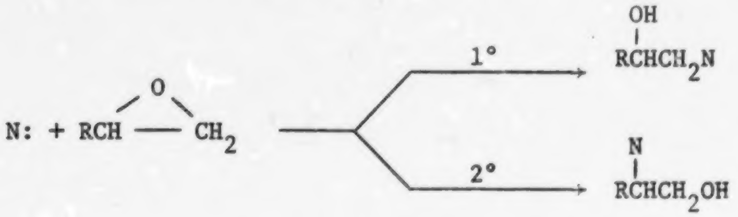
d) Diepoxybutane

No information was available on domestic use of diepoxybutane. IARC (1976) reports use of the compound in some countries for polymer curing, crosslinking textile fibers, and as an antimicrobial agent to prevent spoilage.

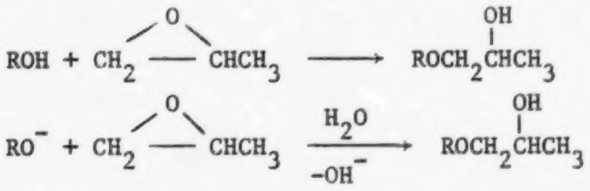
2. Chemistry Involved in Use

Most epoxides are consumed as chemical intermediates in synthesis of a variety of products, some of which are finished products while others are further processed before marketing. The parent epoxides are used directly in only a few applications, the largest of which is the approximately 4 million lbs of butylene oxide added to chlorinated solvents as a stabilizer. The chemistry important in epoxide use primarily involves ionic reactions which open the epoxide ring. The chemistry discussed herein is centered upon ethylene oxide and propylene oxide, since they are the most important commercially. Reactivities of propylene and butylene oxide are virtually identical.

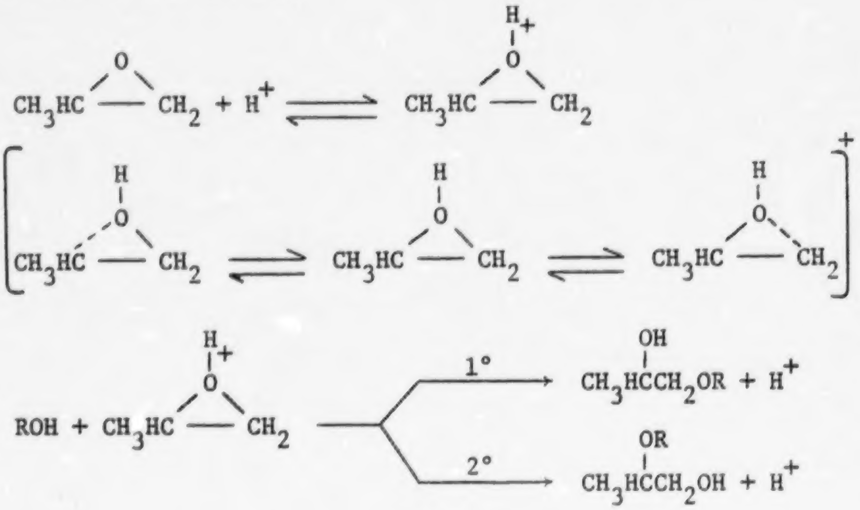
The epoxides are a class of ethers and their reactions with ionic substrates conform to the general behavior of other ethers. The typical ionic reaction cleaves one of the carbon-oxygen bonds of the oxirane ring and forms a new bond between the carbon and a nucleophile. Reaction pH is critical since it affects reaction mechanism and kinetics (discussed in more detail for hydrolysis in Section II.C.3). The pH can affect product distribution from ambident epoxides (March, 1977; Lapkin, 1965), which are those epoxides containing nonequivalent carbon-oxygen bonds. Since propylene oxide and butylene oxide are ambident epoxides, nucleophiles can react with them at either the primary (1°) or secondary (2°) carbon atom:



Ethylene oxide is non-ambident, so only one structural isomer is possible. The pH affects reaction rate and products in part by altering mechanisms. In neutral or alkaline conditions the epoxide is cleaved by an S_N2 mechanism (bimolecular nucleophilic substitution); alkaline conditions can affect reaction rates by increasing nucleophilicity of substrates that can ionize. In substrates such as alcohols, the alkoxide ion (RO^-) reacts faster than the parent alcohol (ROH). In either neutral or alkaline conditions the epoxide is cleaved only at the primary position, where steric hindrance is least:

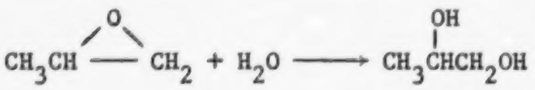


Epoxide reactions in acidic solutions follow more complex pathways, which are interpreted mechanistically as intermediate between A-1 and A-2 (see the discussion on hydrolysis in Section II.C.3) (Long and Pritchard, 1956). The reaction is consistent with the following:

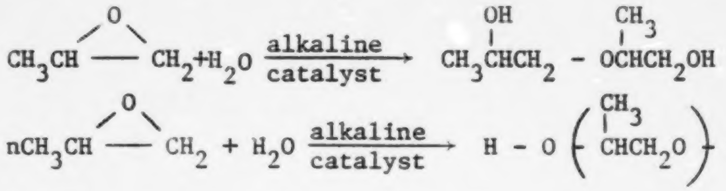


In summary, ionic reaction rates are controlled by the carbon-oxygen bond cleavage. The reactions are acid catalyzed and with nucleophiles that yield anions, the reactions are alkaline catalyzed; also, only one product (1° substitution) is expected with reaction in neutral or alkaline systems but two products (1° or 2° substitution) can occur with acid catalysis.

Most of the commercial processes using epoxides as synthesis intermediates involve their reactions with water or hydroxyl-containing organic substrates, which include alcohols, phenols, and carboxylic acids. The reactions are all accelerated by general acid or base catalyses. Glycol preparation requires epoxide hydrolysis in a dilute aqueous solution:

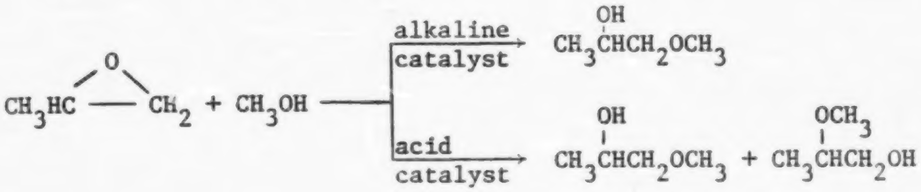


Di-, tri-, and polyglycols are prepared by increasing the concentration of the epoxide or altering the nature of the catalyst and/or solvent systems. Alkaline catalysts generate oligimers and polymers with head-to-tail structure (Lapkin, 1965):



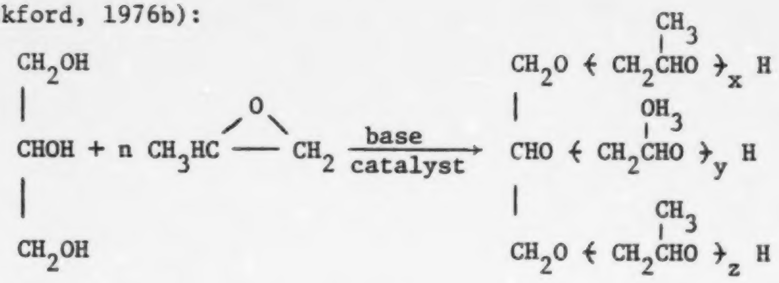
These polymers have a largely isotactic structure (head-to-tail polymerization) but selectivity is not 100%. Since the alkaline hydrolysis of epoxides proceeds with a high retention of configuration at the asymmetric carbon atom (see Section I.A.1), optically active propylene oxide can be polymerized to produce an optically active polymer. According to Lapkin (1965) acid catalysis of the propylene oxide polymerization yields polymers indistinguishable from those prepared by alkaline catalysis. Copolymers of ethylene oxide and propylene oxide have been prepared with each other and with other epoxides (e.g., 4-vinylcyclohexene dioxide) or olefins (e.g., ethylene or vinylidene chloride). The polymerization initiators and conditions are chosen for selective polymer characteristics. Catalysts utilized have included Bronsted acids (H^+), Lewis acids (iron salts, BF_3, etc.), organometallics, and metallic hydroxides (in homogeneous solution, as emulsion, and as solid).

Epoxides are reacted with alcohols to yield monoethers. The reactions of methanol with propylene oxide illustrates ether formation (Jefferson Chemical Co., undated b):



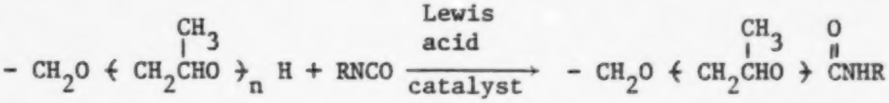
Polyether glycols are prepared by reacting polyols (e.g., glycerine or sorbitol) with solutions containing high epoxide concentrations

(Blackford, 1976b):



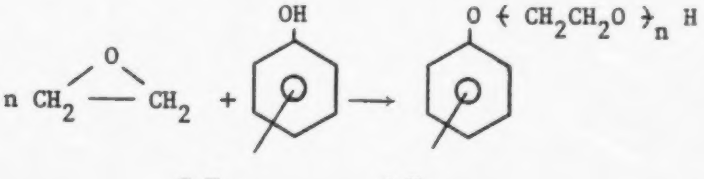
(n = x + y + z)

In urethane preparations the polypropylene and polyethylene glycols are reacted with isocyanate:

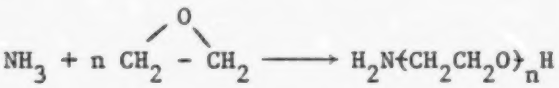


$$-CH_2O(CH_2\overset{CH_3}{\overset{|}{C}}HO)_nH + RNCO \xrightarrow[\text{catalyst}]{\text{Lewis acid}} -CH_2O(CH_2\overset{CH_3}{\overset{|}{C}}HO)\overset{O}{\overset{\|}{C}}NHR$$

Glycol esters of carboxylic acids and phenols and ethers of cellulose, starch, and other polyols are also prepared as described above. For example, reaction of ethylene oxide and nonylphenol yields nonylphenoxypolyethoxyethanol, a non-ionic, surface-active agent (Blackford, 1976b):

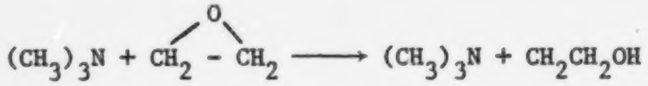


The epoxides react with amines by pathways similar to reactions with hydroxyl compounds. Reaction of ethylene oxide and ammonia yields the commercially important ethanolamines:



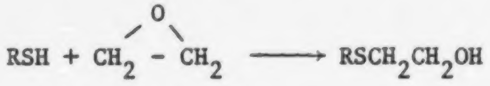
where n is typically 1 to 4.

Choline is prepared by reacting trimethylamine with ethylene oxide (Jukes, 1964):

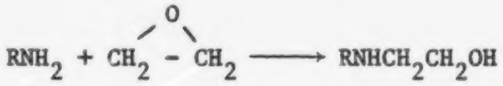


$$(CH_3)_3N + \overset{O}{CH_2 - CH_2} \longrightarrow (CH_3)_3N + CH_2CH_2OH$$

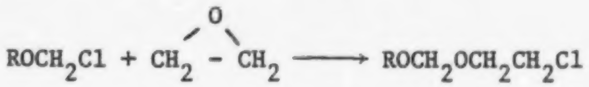
Other ionic reactions of the epoxides include the following (Lapkin, 1965; Jefferson, undated a and b; March, 1977; Schultze, 1965):



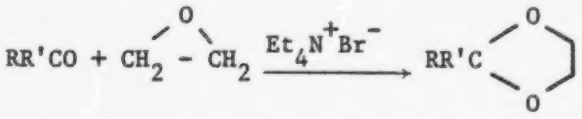
$$RSH + \overset{O}{CH_2 - CH_2} \longrightarrow RSCH_2CH_2OH$$



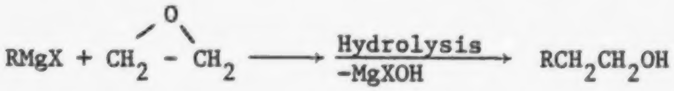
$$RNH_2 + \overset{O}{CH_2 - CH_2} \longrightarrow RNHCH_2CH_2OH$$



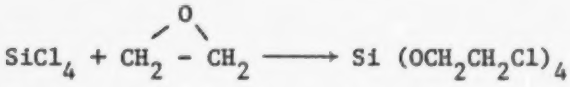
$$ROCH_2Cl + \overset{O}{CH_2 - CH_2} \longrightarrow ROCH_2OCH_2CH_2Cl$$



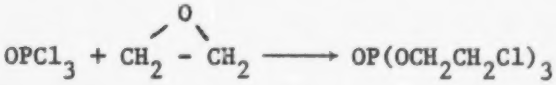
$$RR'CO + \overset{O}{CH_2 - CH_2} \xrightarrow{Et_4N^+Br^-} RR'C$$



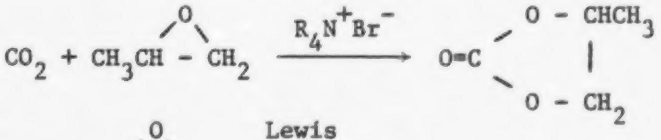
$$RMgX + \overset{O}{CH_2 - CH_2} \longrightarrow \xrightarrow[-MgXOH]{Hydrolysis} RCH_2CH_2OH$$



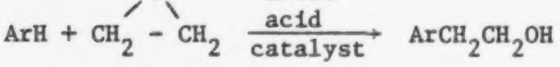
$$SiCl_4 + \overset{O}{CH_2 - CH_2} \longrightarrow Si\ (OCH_2CH_2Cl)_4$$



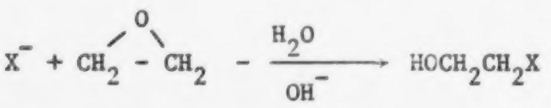
$$OPCl_3 + \overset{O}{CH_2 - CH_2} \longrightarrow OP(OCH_2CH_2Cl)_3$$



$$CO_2 + \overset{O}{CH_3CH - CH_2} \xrightarrow{R_4N^+Br^-} O{=}C\begin{matrix} O - CHCH_3 \\ | \\ O - CH_2 \end{matrix}$$



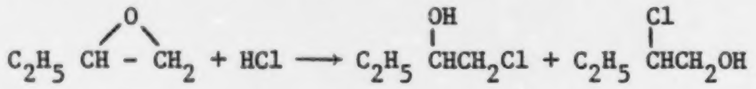
$$ArH + \overset{O}{CH_2 - CH_2} \xrightarrow[catalyst]{\substack{Lewis\\ acid}} ArCH_2CH_2OH$$



$$X^- + \overset{O}{CH_2 - CH_2}\ - \xrightarrow[OH^-]{H_2O} HOCH_2CH_2X$$

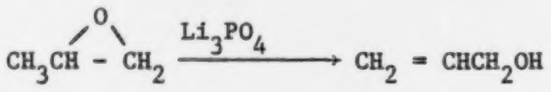
where X is inorganic ions such as Cl^-, CN^-, CNS^-, etc.

Butylene oxide is added to chlorinated solvents to scavenge HCl liberated by solvent degradation. The scavenging reaction is



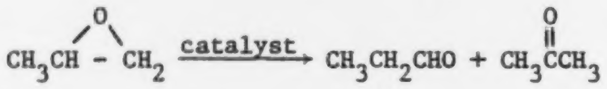
$$C_2H_5\overset{O}{CH-CH_2} + HCl \longrightarrow C_2H_5\overset{OH}{\overset{|}{C}}HCH_2Cl + C_2H_5\overset{Cl}{\overset{|}{C}}HCH_2OH$$

Propylene oxide is isomerized by thermal or by catalytic activity. Catalytic isomerization is used in the commercial manufacture of allyl alcohol (Oosterhof, 1976). The conversion is almost quantitative with Li_3PO_4:



$$CH_3\overset{O}{CH-CH_2} \xrightarrow{Li_3PO_4} CH_2 = CHCH_2OH$$

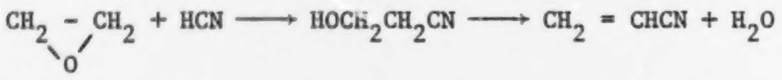
Isomerization of propylene oxide over Al_2O_3 or pumice at 500°C yields a mixture of propionaldehyde and acetone (Jefferson, undated b; Horsley, 1968):



$$CH_3\overset{O}{CH-CH_2} \xrightarrow{catalyst} CH_3CH_2CHO + CH_3\overset{O}{\overset{\|}{C}}CH_3$$

3. Discontinued Uses of Epoxides

Until 1953 (when acetylene was first used), all acrylonitrile was produced by the catalytic dehydration of ethylene cyanohydrin that was prepared from ethylene oxide and hydrogen cyanide. The reaction may be represented as follows:

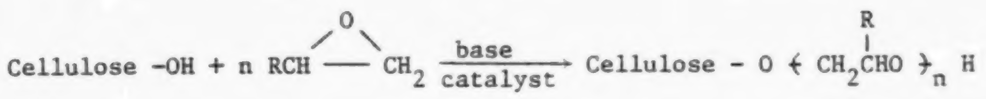


$$\underset{O}{CH_2-CH_2} + HCN \longrightarrow HOCH_2CH_2CN \longrightarrow CH_2 = CHCN + H_2O$$

In 1956, American Cyanimid Company closed down its 35 million lbs per year plant at Warners, New Jersey, which was based on this process. From then to 1966 when it was discontinued this process was used only by Union Carbide at Institute, W. Virginia (Blackford, 1974), In 1965, Union Carbide consumed 90 million lbs of ethylene oxide to make acrylonitrile. No other significant discontinued uses of the epoxides under consideration are known.

4. Projected or Proposed Uses

Wood treatment is a potentially important market for epoxides (Anon., 1977d). The USDA Forest Product Laboratory has reported that treating southern yellow pine with epoxides (including ethylene oxide, propylene oxide, and butylene oxide) improves its durability. The treatment adds 20% to 30% (by weight) of the epoxide to the wood. A mild alkaline catalyst (typically trimethyl or triethyl amine) catalyzes the initial reaction of the epoxide with cellulose hydroxyl groups and the polymerization reactions of the epoxide (Rowell and Gutzmer, 1975; Rowell *et al.*, 1976):



The treatment is facile at 120°C and 150 psi with triethylamine catalysis. Required treatment time increased with molecular weight for the above three epoxides; butylene oxide required 4 hours for a 25% weight addition, while under the same conditions propylene oxide yielded a 32.5% weight addition after one hour. The treated wood had improved dimensional stability (shrinkage and swelling as the result of weathering effects were less) and was resistant to degradation by fungi or by termites. This treatment did not yield any reaction by-products and residual epoxide and catalyst were easily removed. The bonding of the polyethers to the treated wood was stable.

Other projected and proposed uses have minor potential market impact in comparison to the proposed use for wood treatment. Most represent expansions of existing markets rather than new applications. Extentions of current uses include new applications of propylene oxide and ethylene oxide for disinfecting dried foods, packaging materials, surgical equipment and other materials requiring disinfection (Hart and Brown, 1974; Tompkin and Stozek, 1974; Alguire, 1973). Commercial literature from epoxide manufacturers suggest some reactions of epoxides which could be applied to new products, and new applications of existing products. Butylene oxide has been suggested as an intermediate for nonionic emulsifiers and detergents, petroleum demulsifiers, oil additives, lubricants, textile chemicals, and similar products (Lapkin, 1965). Additionally, butylene oxide could have some use in production of polyether polyols (Lawler, 1977).

5. Alternatives to Uses for Epoxides

a) Butylene Oxide

More than 95% of butylene oxide annually produced is used as a stabilizer in chlorinated solvent such as 1,1,1-trichloroethane and trichloroethylene. Other chemical compounds, which have been patented for use as stabilizers in these chlorinated solvents, include glycol diesters, ketones, nitriles, dialkyl sulfoxides, imines, dialkyl sulfides, dialkyl sulfites, tetraethyl lead, morpholine, nitroaliphatic hydrocarbons, 2-methyl-3-butyn-2-ol, _tertiary_-butyl alcohol, tetrahydrofuran, 1,4-dioxan, _sec_-butyl alcohol, and monohydric acetylenic alcohols (Whetstone, 1964). Butylene oxide is apparently used because it is the best available commercial compound for these applications in terms of usefulness and economics, but industry could find a suitable replacement stabilizer if butylene oxide was no longer available.

b) Ethylene Oxide

More than 99% of the U.S. production of ethylene oxide is used as a chemical intermediate in chemical syntheses of glycols and other compounds. Alternatives would require production routes from raw materials other than ethylene oxide.

Roughly 63% of the ethylene oxide production is hydrolyzed to ethylene glycol. A new process for making ethylene glycol directly from ethylene has been developed by Halcon, Inc. (Klapproth, 1976). Ethylene is reacted with acetic acid in the presence of a catalyst to form mono- and diacetates, which are then hydrolyzed to ethylene glycol. Oxirane Corp. has constructed an 800 million lb per year plant based upon this technology in Channelview, Texas. This capacity represents roughly 25% of the total industry ethylene glycol capacity.

In the past, there have been other commercial routes to ethylene glycol. In 1968, the DuPont Chemical Company shut-down a plant that used a methanol-to-formaldehyde-to-glycolic acid-to-ethylene glycol route. At one time, ICI United States Inc. manufactured ethylene glycol by the hydrogenation and hydrolysis of carbohydrate feedstock (e.g., molasses); the plant is now on standby. Prior to 1973, Celanese Corp. obtained small quantities from the vapor-phase oxidation of propane (Klapproth, 1976).

As far as the other compounds synthesized from ethylene oxide are concerned, no information was available on syntheses from other raw materials.

Relatively small quantities of ethylene oxide, roughly 0.1 million lbs annually (Dow Chemical estimates that the volume of ethylene oxide used as a fumigant is less than 0.2% of total production which in 1978 would equal 10 million lbs - Kurginski, 1979), are used for fumigant purposes. Since there are many commercial fumigants available, it seems likely that many of its fumigant uses could be replaced by an alternative fumigant.

c) Propylene Oxide

Since nearly all propylene oxide is consumed in chemical synthesis, alternatives require different compounds as raw materials for production. Currently, there are no commercially viable alternative routes for the formation of the derivatives normally made with propylene oxide.

Until 1970 the Chemicals Division of Atlas Chemical Ind. (now ICI United States) produced propylene glycol by the hydrogenation and hydrogenolysis of molasses at it's 5 million lbs per year plant in Atlas, Delaware (Blackford, 1976b). This plant is no longer producing propylene glycol.

There is no information available in the literature on propylene glycol production from propylene and acetic acid in a manner similar to the direct production of ethylene glycol from ethylene as discussed above.

The small amounts of propylene oxide used as fumigant could likely be replaced by some other commercial fumigant.

C. Entry Into the Environment

Sparse information was available on entry of the subject epoxides into the environment. The potential for entry was assessed from the engineering aspects of the manufacture, handling and transport, use and disposal, and from the properties of the selected epoxides.

1. Points of Entry

a) Production

i. Ethylene Oxide

Ethylene oxide is mainly made by direct oxidation of ethylene (see Section II.A.3). The process consists of vapor phase oxidation of the ethylene, followed by adsorption and wash of the effluent gases in water, and then by vacuum stripping and fractionation of the ethylene oxide. Ethylene oxide can be lost from the vapor phase as fugitive emissions or with vented gases. No information was available on its possible loss with waste waters or with any solid wastes. Since ethylene oxide vapor pressure is high, atmospheric emissions appear a more likely environmental entry than waste disposal.

Pervier and coworkers (1974) surveyed air emissions from ethylene oxide production plants and estimated a total annual emission of air pollutants of 120 million lbs by 1980. The emissions had the following composition:

hydrocarbons	118.6 million lbs
nitrogen oxides	0.45 million lbs
sulfur oxide	0.14 million lbs

Most of the emissions are released by vents on process equipment. They reported no details on the contribution of ethylene oxide to this total. Most of the emission appears to be ethylene gas. Dow Chemical (Kurginski, 1979) indicates that these emissions appear to be out of date and are at least 20 times too high. They estimated that less than 5 million lbs of ethylene oxide is released annually during production and processing.

Potential contaminant releases from chlorohydrination procedure is discussed below. This route provides only a small amount of the ethylene oxide manufactured each year (see Section II.A.2).

ii. Propylene Oxide

The chlorohydrination route is currently the principal method for propylene oxide manufacture. The propylene oxide is produced in aqueous solution and is separated by distillation (see Section II.A.3). The most probable release is into the atmosphere through fugitive emissions and with vented gases. The process generates about 45 to 50 tons of waste water per ton of propylene oxide produced (Kurginski, 1979; Anon., 1978b). Its treatment is discussed below (see Section III.C.3).

Propylene oxide is also manufactured by a peroxidation procedure. The process has a similar potential for emission of propylene oxide as via chlorohydrination during its separation from the liquid phase but waste water and by-product generation is significantly less.

iii. Butylene Oxide

The production of butylene oxide and its potential release to the environment will be similar to propylene oxide (see Section II.A.3).

b) Handling, Transport, and Storage

The selected epoxides could be emitted to the atmosphere as the result of fugitive emissions or venting during their handling, transport, or storage. No specific information was available to describe these losses. Information on current practices, procedures or environmental controls was sparse and no monitoring information was available. The following paragraphs discuss potential releases of epoxides without making any attempt to establish relative importance.

Bulk shipments of ethylene, propylene, and butylene oxide are commonly made by railroad freight tanker; the sizes of the tankers are commonly 10,000 and 20,000 gallons. Shipments of these oxides are also made in special 55-gallon drums and by highway truck tankers. The epoxides are stored in bulk containers as well as in smaller quantities in 55-gallon drums.

No information was available on the usual emission controls used on storage and transport containers. "Padded" containers, if used, would conserve vapors which would otherwise be vented to the atmosphere. Emissions could also occur during equipment purging in routine maintenance, gauge glass blowdown or leaks.

Release is possible during transfer of the selected epoxides. In normal practice railway tankers are loaded and unloaded directly from or into storage tanks. The transfer utilizes nitrogen pressurization to approximately 50 psi or pumping. Faulty equipment or over-pressurization can cause epoxide emissions. Small amounts spilled during handling could also release small amounts of epoxides.

A major concern is release from a storage container or transport-related accident. This could vary in scope from a relatively minor incident, such as release through pressure safety valve or rupture disc, to a major accident in which an entire storage container or tanker would rupture. No information was available to predict how often the minor release accidents do, in fact, occur or on the amount of epoxides they annually release. Although none of the selected epoxides appear directly involved with previous, major accidents, the potential is present.

c) From Use

i. Ethylene Oxide

Most ethylene oxide is used in chemical syntheses of various compounds. The potential for environmental exposure of ethylene oxide during syntheses use is, perhaps, equivalent to the potential for release during production as discussed above.

Small amounts of ethylene oxide are consumed as a fumigant, as a food and cosmetic sterilant, and in hospital sterilization. In 1975, an estimated 0.1 million lbs of ethylene oxide were used for these fumigant purposes (Landels, 1976) while it would appear to be 10 million lbs according to Dow Chemical Co., (Kurginski, 1979). All of the ethylene oxide used as a fumigant enters the environment (soil, food products, and air) and also presents a potentially serious hazard to the applicators.

ii. Propylene Oxide

Like ethylene oxide, most propylene oxide is used in chemical syntheses and potential for environmental exposure is perhaps the same as for production. Propylene oxide is also used as a fumigant like ethylene oxide. Therefore, similar exposure potentials exist.

iii. Butylene Oxide

Most butylene oxide is used as a stabilizer in chlorinated solvents, such as trichloroethylene and methyl chloroform. These chlorinated solvents are, in turn, primarily used for metal cleaning and vapor degreasing of metal parts. Under these circumstances, direct environment escape during use is a real possibility.

d) From Disposal

About 99% of the epoxides produced in this country are used to make other chemicals, so only a small fraction of the total production could possibly be released to the environment from disposal. Excess or unwanted ethylene and propylene oxide which were to be used as fumigants and the butylene oxide which may be disposed in chlorinated solvents are possible exceptions.

The potential emissions of process wastes generated from manufacture or from use as an intermediate of the selected epoxides is discussed below.

2. Disposal Methods, Emission Controls, and Effluent Controls

Atmospheric emissions of the epoxides through process vents appear the most important source of their release to the environment. Incineration appears the method applied for emissions control. Moore and Frisch (1971) reported that catalytic combustion is applied to ethylene oxide tail gas from scrubbing operations. No information was available concerning other emission controls for epoxides from manufacturing or use. Catalytic oxidation does appear to be another choice for emission control (Moore and Frisch, 1971; Spencer, 1971).

Storage, transport, and handling methods have been extensively described in literature supplied by manufacturers (BASF Wyandolte Corp, 1972; Dow Chemical Company, 1977; Jefferson Chemical Company, undated a, undated b; Oxirane Chemical Company, undated) and safety information sources (NFPA, 1975; MCA, 1971). This literature chiefly concerns safety of humans and property. Tank cars for ethylene oxide and propylene oxide are specified as ICC-105A100W and 105A100. These are equipped with pressure relief valves which vent excessive pressure into the atmosphere. The epoxides should preferrably be stored in an area detached from the plant site and storage tanks should be diked. Ethylene oxide should be equipped with cooling pipes. Tanks must be equipped with pressure relief valves, but specific instructions on emission control of excess pressure was not included. Vapor recompression systems could be applied to prevent emissions (Spencer, 1971).

Process waters for ethylene oxide manufacture and use appear to be minor problems with respect to waste treatment. The process water is recycled in its manufacture and its primary use as an intermediate in ethylene glycol manufacture (Sittig, 1962, 1965). No information was available on how much of the process water eventually is treated and no specific details were provided on treatment methods. The waste water will contain high BOD, but inorganic composition and refractory organics appear minimal problems with ethylene oxide manufacture or ethylene glycol production from ethylene oxide (Sittig, 1962, 1965; Spencer, 1971). Conventional water treatment (including filtration and flocculation) with a biological treatment appears sufficient (Spencer, 1971; Shenderova _et al._, 1972). Patents (Kadoi and Kataoki, 1968;

Ishishi and Kobayashi, 1973) describe physical-chemical treatments with saponification, neutralization, and active carbon filtration for epoxide waste water treatment.

The environmental problem from propylene oxide manufacture via chlorohydrination is caused by the large amounts of by-products formed. The process generates about 60 tons of calcium chloride-containing waste water per ton of propylene oxide (Anon., 1978b). In addition, various chlorinated organic by-products are formed. Little, if any, residual propylene oxide is in the waste water. The waste water effluent is unsuitable for disposal directly into natural drainage and will not be accepted in municipal sewage systems without expensive pretreatment (Hancock, 1973). There is only a limited market for the organic chlorinated by-products, and disposal of them may sometimes be a problem. One of the major producers of propylene oxide via the chlorohydrin route reportedly collects and burns most of the by-product bis(2-chloro-1-methylethyl)ether (SRI, 1977).

There is currently a proposed solution to the calcium chloride-waste water effluent disposal problem (Anon., 1978b). The C-E Lummus Company has demonstrated on a laboratory scale that the calcium chloride (or sodium chloride) brine solution can be fed to an electrolytic diaphram cell to regenerate chlorine gas and caustic, which is used in the propylene oxide manufacture process. Currently, this proposed solution to the propylene oxide waste water problem appears to be feasible, but full-scale commercial trials have not been made.

No specific solid wastes are associated with manufacture of the selected epoxides. Ethylene oxide manufacture does utilize a solid catalyst, which must be periodically replaced. Because the silver catalyst is expensive, it is regenerated rather than disposed. Information was not available on solid waste generation from all uses of the selected epoxides. The major uses, as chemical intermediates, will sometimes have heavy ends from distillation pots which require disposal. Incineration appears the method of choice (Spencer, 1971) but no information was available on actual practices.

The recommended methods for disposal of unwanted epoxide is either dilution with large amounts of water (to prevent fire hazard) or controlled incineration (BASF, 1972; MCA, 1971; Spencer, 1971). Disposal with water could allow entry of the corresponding glycol into the environment.

3. Potential Production in the Environment

The major source of potential inadvertent production in the environment of the considered epoxides is probably the combustion of hydrocarbon fuels. Hughes _et al_. (1959) utilized gas-liquid partition chromatography to separate and identify oxygenated derivatives of hydrocarbons which were found in the combustion products of hydrocarbon fuels. Among the oxygenated combustion products identified were ethylene oxide and propylene oxide. Barnard and Lee (1972) identified these compounds in the oxygenated combustion products from _n_-pentane combustion. It is conceivable that quantities of ethylene oxide and propylene oxide, which may approach millions of lbs, are annually emitted in automobile exhaust. Stationary sources of hydrocarbon combustion may also emit large quantities of these compounds into the environment.

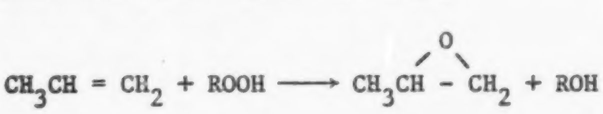
Ethylene oxide has been identified in tobacco smoke (Binder and Lindner, 1972; Binder, 1974). It is not uncommon for tobacco to be treated with ethylene oxide by cigarette manufacturers for its fumigant properties.

Binder and Lindner (1972) determined that the ethylene oxide concentration of unfumigated tobacco was 0.02 μg/ml, while fumigated tobacco had a concentration of 0.05 μg/ml and extensively fumigated tobacco had a concentration of 0.30 μg/ml. Binder (1974) determined the ethylene oxide content of smoke from unfumigated tobacco as 1 μg/g.

DeBont and Albers (1976) have concluded that ethylene oxide is a product of ethylene catabolism by the ethylene-oxidizing strain E20 bacterium.

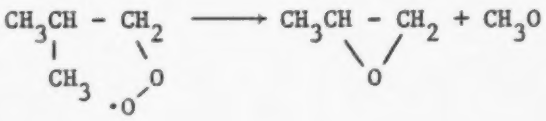
Sato and Cvetanovic (1958) have reported that butylene oxide is formed by the photooxidation of 1-butene by nitrogen dioxide. Both of the compounds, 1-butene and nitrogen dioxide, are emitted in substantial amounts by automobile exhaust. There may be a very slim chance that two compounds could react by photooxidation in the atmosphere to produce butylene oxide.

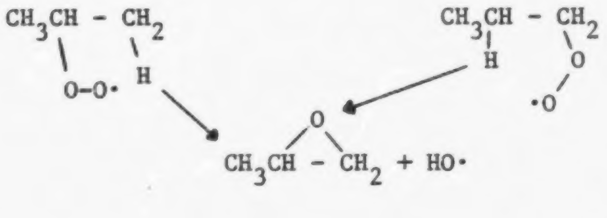
The epoxides are formed in the photochemical smog cycle. Olefins can be converted to the corresponding epoxides by reaction with an organic peroxide (Altshuller and Buffalini, 1965).



$$CH_3CH = CH_2 + ROOH \longrightarrow CH_3\overset{O}{CH - CH_2} + ROH$$

Alkyl peroxides can decompose to yield an epoxide and oxy radical (NAS, 1976).





Water disinfection has the potential to convert olefins to epoxides. Olefin conversion during chlorination would proceed by the same route as for chlorohydrination production of the epoxide. The olefin would first be converted to the chlorohydrin (Morris, 1975; Carlson and Caple, 1977). The subject epoxides would only form by alkaline-catalyzed cyclization. Cyclization would not occur in neutral solution for the precursors of the subject epoxides; instead, those chlorohydrins would hydrolyze directly to yield glycols (Frost and Pearson, 1961). Epoxides could form during ozonation, also (Carlson and Caple, 1977). The epoxidation is a secondary reaction in which aqueous organics are first converted by ozone to peroxides and resultant peroxide epoxidizes the olefin.

Although water treatment can convert olefins to epoxides, this route is probably not important with respect to the selected epoxides. This conclusion is based upon the low solubilities and high vapor pressures of the precursor olefins. Also, the hydrochlorination route for epoxide formation is unlikely unless it is performed at an unusually high pH. These factors limit ambient concentrations of the olefins in environmental waters.

D. Environmental Pathways and Fate

The epoxides are not persistent in the environment. Available information on their chemical and biological properties characterize them as highly reactive. The available information on transport was not sufficient to develop a definite description of transport characteristics. Interphase transport from water to air seems a slow process, but evaporation of ethylene oxide applied as a sterilant or a fumigant appears to be an important process. High water solubility and high vapor pressure result in significant mobility of the epoxides within water or air.

1. Transport Within and Between Media

No specific information on environmental transport was available for any of the selected epoxides. Chemodynamic relationships applied to known physical properties (see Table 2) permit some insight into the transport behavior (Freed *et al.*, 1977).

Ethylene oxide, propylene oxide, and butylene oxide possess high solubilities in water and high vapor pressure (ethylene oxide is a gas at ambient temperature). No information was available on adsorption characteristics with soil, sediments or particulates. Because of their physical properties, these epoxides will undoubtedly move freely within water systems and in the atmosphere and they are likely to migrate rapidly in soil.

A description of intermedia transport is made difficult by the lack of any direct measurements. The only information available consisted of studies of ethylene oxide loss from fumigated materials (see Section II.D.2). Scudamore and Heuser (1971) examined the fate of ethylene oxide in various, treated commodities. They determined that ethylene oxide dissipation was an apparent first order kinetics process. The dissipation rates were measured for some samples stored both in sealed containers and in trays (Table 13). Dissipation rate in open trays will include both vaporization and degradation processes, while sealed containers would measure only degradation. So, vaporization rates can be estimated by differences between the two storage methods:

$$K_{vapor} = K_{trays} - K_{containers}$$

The estimated vaporization rates suggested vaporization half-lives in the range of approximately four hours to 17.5 days. Their data also indicated more rapid vaporization at 25°C than at 10°C, which is expected.

Table 13. Estimated Vaporization Rate for Ethylene Oxide from Commodities (Adapted from Scudamore and Heuser, 1971)

Commodity	Experimental Conditions				Rate of Ethylene Oxide Loss, K ($days^{-1}$)		
	M.C.	c.t.	t_1	t_2	In sealed containers (A)	Spread on open trays (B)	B-A
Semolina	13.6	825	25	25	0.74	>5	>4
Wheat I	14.5	500	25	25	0.62	0.66	0.04
Wheat II	15	1000	25	25	0.45	0.62	0.17
Wheat II	15	1000	25	10	0.09	0.18	0.09
Sultanas	12.5	600	10	10	0.28	0.61	0.33
Sultanas	17	600	25	25	1.2	1.8	0.6
Cocoa beans	5	600	10	10	0.24	1.5	1.26
Ground nuts	7	500	25	10	0.22	0.43	0.21
Ground nuts	7	500	25	25	0.78	1.72	0.94

MC = moisture content (%)
c.t. = EO concentration-time product (mg h/ℓ)
t_1 = Gas treatment temperature (°C)
t_2 = Storage temperature (°C)

A study by Alguire (1973) on dissipation of ethylene oxide from treated packaging materials demonstrated rapid vaporization. The salient study concerned ethylene oxide dissipation from polystyrene creamer cups, Figure 7. The vaporization half-life was less than one day. No other direct information on ethylene oxide evaporation was available (see Section II.D.2.c).

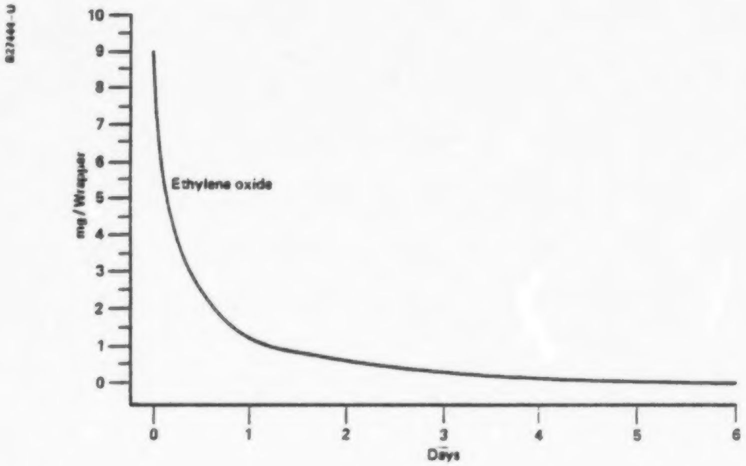


Figure 7. Dissipation of ethylene oxide following gas treatment of polystyrene creamer cups (from Alquire, 1973).

The rate for epoxide evaporation from water cannot be adequately estimated from the information available. This rate can be derived from the Henry's Law Constant, H, but only for substrates of low water solubility (Mackay and Leinonen, 1975; Dilling, 1977). Since the epoxides are very soluble, calculation of evaporation rate and half-life by the Dilling approach is suspect. Henry's Law Constant could not be calculated for ethylene oxide because it is completely miscible with water, but was calculated as 2.8×10^{-4} and 7.6×10^{-4} at 25°C for propylene oxide and butylene oxide, respectively, from the data of Table 2. Based upon the Henry's Law Constants, a low rate of epoxide evaporation is speculated. Epoxide hydrolysis rates (see Section II.D.2.1) seem competitive with evaporation rates.

2. Chemical and Biological Degradation

Epoxide degradation has been fairly well characterized. The selected epoxides are reactive in all media. Available information on their ionic reactions indicate that chemical and biological degradation follow parallel pathways with respect to products. Their degradation in water, soil, commodities, and manufactured products proceed through ionic reactions. Their degradation in the atmosphere has not been well characterized with respect to products. Available information indicates that they are very reactive in photochemical smog cycle reactions. No information was available on whether ionic reactions (e.g., with water vapor or water within aerosols) significantly contributed to their degradation in the atmosphere. The information on epoxide degradation is discussed in four sections: a) degradation in water; b) degradation in soil; c) degradation in commodities and manufactured products; and d) atmospheric degradation.

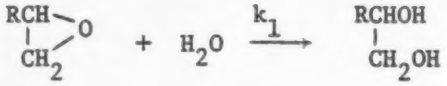
a) Degradation in Water

The epoxides degrade in water by hydrolysis and related ionic reactions. The chemistry involves cleaving a carbon-oxygen bond of the cyclic ether. This reaction has been studied in great detail by organic chemists and extensive descriptions have been published which are primarily concerned with the mechanism by which the epoxide ring is opened. Since a complete description of all the work is beyond the scope of this present work, the evaluation of the mechanistic papers, herein, is limited to their description of degradation kinetics and products.

Brönsted and coworkers (1929) first noted the pathways for ethylene oxide hydrolysis in aqueous hydrochloric acid some 50 years ago. They described hydrolysis as a combination of a noncatalytic reaction (herein referred to as the spontaneous hydrolysis) and an acid-catalyzed hydrolysis. Reaction with chloride paralleled hydrolysis; chloride and epoxide reacted without catalysis and with acid catalysis.

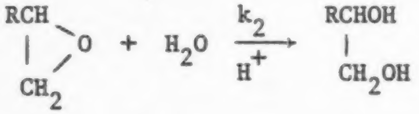
Later work has extended and refined the description of Brönsted and coworkers. Long and Pritchard (1956) demonstrated that epoxide hydrolysis was base catalyzed also. For any epoxide the degradation pathways are as follows for the spontaneous (I), acid-catalyzed (II), and alkali catalyzed hydrolyses (III):

(I)



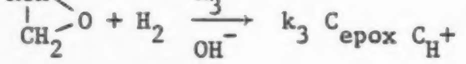
$$\text{Rate} = \frac{-dCepox}{dt} = k_1 \, C_{epox}$$

(II)



$$\text{Rate} = \frac{-dC_{epox}}{dt} = k_2 \, C_{epox} \, C_{H^+}$$

(III)



$$\text{Rate} = \frac{-dC_{epox}}{dt} = k_3 \, C_{epox} \, C_{OH^-}$$

Table 14 summarizes hydrolysis data for the epoxides. The chemical hydrolysis in the environment is expected to proceed primarily by the spontaneous hydrolysis

Table 14. Hydrolysis Kinetics of Selected Epoxides*

Epoxide	Temperature °C	Specific Rate Constant $10^6 k_1$ sec^{-1}	$10^3 k_2$ ℓ/mol-sec	$10^4 k_3$ ℓ/mol-sec
Ethylene oxide	1.0		0.579[d]	
	10.1		8.46[d]	
	30.0		16.9[d]	
	40.0		43.6[d]	
	20	0.36[a]	5.33[a]	
	25	0.556[c], 0.58[e]	9[c]	1.0[f], 1.1[c]
	60	19.2[c]		
	70	43.9[c]		
Propylene oxide	1.0		2.79[d]	
	10.1		8.46[d]	
	30		74.5[d]	
	40		199[d]	
	25	0.69[e]		0.87[f]
	37	2.22[b]	124[b]	2.75[b]
	60	21.1[e]		
Diepoxybutane	37	2.1-1.4[b]	1.94	

* k_1, k_2, and k_3, are described in the text.

(a) Brönsted *et al.*, 1929.
(b) Ross, 1950
(c) Long and Pritchard, 1956
(d) Long *et al.*, 1957
(e) Koskikallio and Whalley, 1959
(f) Pritchard and Siddigui , 1972

pathways. At ambient temperature (25°C) the half-lives for propylene oxide and ethylene oxide were 3.6 days and 13.8 days, respectively, for spontaneously hydrolysis.

Diepoxybutane exists as two isomers (d,l and meso). The separate epoxide groups of each hydrolyze at different rates. Ross (1950) observed a large variation in hydrolysis rates for diepoxybutane; initial hydrolysis rate (15% to 28% epoxide reacting) was 1.9×10^{-6} sec $^{-1}$ while the rate later (68% epoxide reacting) was 1.22×10^{-6} sec. This difference probably arises as the result of the variation in hydrolysis rates of the two epoxide functions. A group at the Southern Regional Research Laboratory, USDA (Benerito et al., 1964, 1969; Ziifle et al., 1965) has investigated diepoxybutane hydrolysis in acid and alkaline systems. Table 15 summarizes alkaline hydrolysis rates for d,l and meso-diepoxybutane. These rates were measured with a heterogenous system composed of aqueous sodium hydroxide and carbon tetrachloride, which measured the partition of the diepoxybutanes between the two phases and the hydrolysis rate in the aqueous phase. Some difference in specific rate constants might occur with a simple aqueous hydrolysis. At ambient temperature the specific rates were measured as $0.9\text{-}4.7 \times 10^{-4}$ ℓ/mole-sec and $3.0\text{-}5.7 \times 10^{-4}$ ℓ/mole-sec, respectively, which are values in the same range as those measured for alkaline hydrolyses of propylene oxide and ethylene oxide. Benerito et al. (1964) did not distinguish between hydrolysis rates for the first or second epoxide ring. Acid-catalyzed hydrolysis kinetic measurements showed no difference for specific rate constants of meso or d,l-diepoxybutane, but the two epoxide rings hydrolyze with different specific rates; Table 16 summarizes pseudo-first order rate constants from pH 1.65 to 3.62.

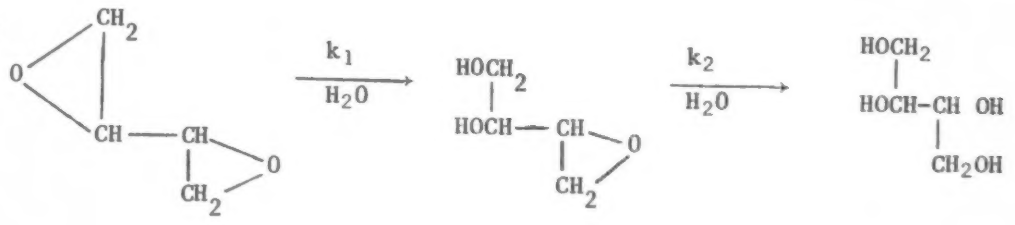
Table 15. Specific Rate Constants for Alkaline-Catalyzed Hydrolysis of Diepoxybutane (Adapted from Benerito *et al*., 1964)

Isomeric Diepoxybutane	Specific Rate Constant at 25°C NaOH, *M*	 10^2k (ℓ/mole-min)
Meso	0.504	2.82
	1.008	2.81
	1.453	2.81
	2.769	2.03
	4.335	1.60
	9.113	0.53
d,l	2.868	1.81
	4.599	3.40

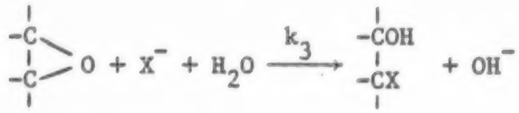
Table 16. Specific Rate Constants for Acid-Catalyzed Hydrolysis of Diepoxybutane (Adapted from Ziifle _et al._, 1965, Benerito _et al._, 1969)

	Specific Rate Constant (Pseudo first-order in min^{-1})*											
Acid	HCl			HBF$_4$								
pH	3.25			3.62			2.65			1.65		
Temperature, °C	10^4k_1	10^4k_2	k_2/k_1	10^4k_1	10^4k_2	k_2/k_1	10^4k_2	10^4k_1	k_2/k_1	10^4k_1	10^4k_2	k_2/k_1
25	0.46	0.11	0.24	--	--	--	7.5	10.8	1.44	64.8	96.0	1.43
40	3.49	0.35	0.10	3.61	1.3	0.7	36.0	58.0	1.61	368	560	1.52
60	19.70	2.97	0.15	18.7	6.4	0.34	170	360	2.12	--	--	--
75	50.08	21.49	0.43	58.7	26.0	0.44	--	--	--	--	--	--
90	320.63	371.16	1.16	--	--	--	--	--	--	--	--	--

*



Epoxides can also react with nucleophiles (anions or Lewis bases) by pathways which parallel hydrolysis (reaction with water or hydroxide). The chemistry, although similar to hydrolysis, is more complex. The epoxide ring can be cleaved by spontaneous reaction or by acid-catalyzed reaction:



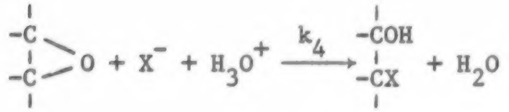


Table 17 summarizes specific rate constants for reactions of the selected epoxides with various anions. Brönsted and coworkers (1929) noted a proportionality between the rate constants for catalyzed and uncatalyzed reactions:

$$\frac{k_2}{k_1} = \frac{k_4}{k_3}$$

Their data was limited to hydrolysis and anion reactions with chloride and bromide at 20°.

Anions can react with the unsymmetrical epoxides to yield two products. With terminal epoxides, the products result from anion attack at the primary carbon atom or at the secondary carbon atom:

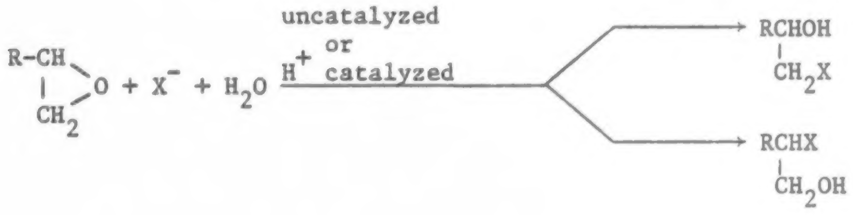


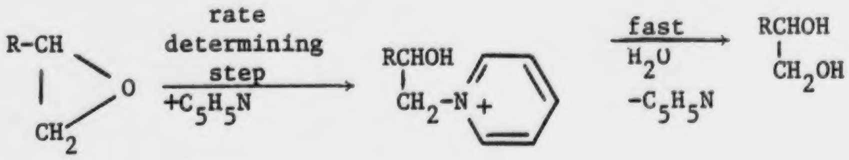
Table 17. Specific Rates of Reaction of Anions and Lewis Bases with Selected Epoxides

Epoxide	Lewis base or Anion	Temperature °C	$10^5 k_3$ (ℓ/mole - sec)	$10^2 k_4$ (ℓ^2/mole^2- sec)
Ethylene oxide	Cl^-	20		2.17 (water)[a]
		25		3.67 (water)[a]
		27		8.23 (50% Aqueous ethanol)[f]
	Br^-	20		8.67 (water)[a]
		25		14.5 (water)[a]
	Pyridine	22	20 (water)[g]	
Propylene oxide	Cl^-	0	517 (THF)[d]	
		20.0	0.259 (9:1 water-dioxane)[c]	10.64 (9:1 water-dioxane)[c]
		30.1	0.728 (9:1 water-dioxane)[c]	30.1 (9:1 water-dioxane)[c]
		40.0	2.14 (9:1 water-dioxane)[c]	81.5 (9:1 water-dioxane)[c]
		27		21.17[b]
	NO_3^-	20.0		0.410 (water)[e]
	OAc^-	37	0.139 (water)[b]	
	Pyridine	22	16 (water)[g]	
	Pyrazine	22	0.29 (water)[g]	
Butylene oxide	Cl^-	40	1.45 (9:1 water-dioxane)[e]	56.6 (9:1 water-dioxane)[e]
Diepoxybutate	OAc^-	37	1.33 (water)[b]	

(a) Brönsted _et al._, 1929
(b) Ross, 1950
(c) Addy and Parker, 1963
(d) Addy and Parker, 1965
(e) Petty and Nichols, 1954
(f) Lamaty _et al._, 1975
(g) Pritchard and Siddiqui, 1972

The product distribution has primarily been studied in research attempts to distinguish mechanisms of epoxide ring opening. The consensus agrees that the spontaneous reaction is S_N2 but disagreement exists whether acid catalyzed epoxide ring opening is A1-like or A2-like (Long *et al*., 1957; Lamaty *et al*., 1975; Pritchard and Long, 1956b; Pritchard and Siddiqui, 1973; Virtanen and Kuokkanen, 1973). A discussion of the mechanism is beyond the scope of this review. Salient information on product distribution for propylene oxide and butylene oxide reaction with chloride is summarized in Table 18. Reaction at neutral (or alkaline) pH yields mainly the secondary alcohol, but it is not quantitative. The production of primary alcohol increases to approximately 35% at pH 3.6 to 3.8.

Some products of epoxide reaction with Lewis bases or with anions are not stable. For example, tertiary amines, such as pyridine, are capable of catalyzing epoxide hydrolysis to glycol:



Aqueous chemical degradation in the environment can be estimated from the contributions of hydrolysis (Equation 1) and anion reactions (Equation 2):

$$\frac{-d\ Cepox}{dt} = (k_1 + k_2\ C_{H_3O^+} + k_3\ C_{OH^-})Cepox \tag{1}$$

$$\frac{-d\ Cepox}{dt} = (k_{3i}C_{Ai} + k_{4i}C_{Ai}C_{H_3O^+})Cepox \tag{2}$$

Table 18. Product Distribution from Unsymmetrical Epoxide Reaction with Chloride* (Adapted from Addy and Parker, 1963, 1965)

Epoxide	Temperature °C	pH	Percentage Product	
			$RCHOHCH_2X$	$RCHXCH_2OH$
Propylene oxide	20.0	7.0	91	9
		4.5	75	25
		3.8	68	32
		3.6	66	34
	30.1	7.0	88	12
		4.5	73	27
		3.8	66	34
		3.6	65	35
	40.0	7.0	86	14
		4.5	72	28
		3.8	64	36
		3.6	64	36
Butylene oxide	40.0	7.0	84	16
		4.5	77	23
		3.8	69	31
		3.6	68	32

* In 9:1 (v/v) water dioxane.

where C_{Ai}, k_{3i}, and k_{4i} refer to the concentration and specific rate constants for each anion or Lewis base. The overall degradation rate is the sum of all contributions; as given in Equation 3

$$-\frac{dC_{epox}}{dt} = [k_1 + k_2\, C_{H_3O^+} + k_3\, C_{OH^-} + \Sigma(k_{3i} + k_{4i}C_{H_3O^+})C_{Ai}]C_{epox} \qquad (3)$$

The initial ratio of an anion substitution product (both possible isomers of an unsymmetrical epoxide) to glycol product can be calculated by Equation 4.

$$\text{Ratio (substitution product:glycol)} = \frac{k_{3i} + k_{4i}C_{H_3O^+}}{k_1 + k_2C_{H_3O^+} + k_3C_{OH^-}} \qquad (4)$$

The relative importance of chemical hydrolysis and reaction with chloride was assessed for ethylene oxide and propylene oxide. Degradation half-lives and product distributions (chlorohydrin to glycol ratios) were estimated for fresh water and marine water (NaCl concentration of 3% or 0.57$\underline{M}$). Specific rates for 25°C were either taken directly or estimated from Tables 14 and 17. The following specific rate constants were utilized:

	Ethylene Oxide	Propylene Oxide
k_1	$0.57 \times 10^{-6}\ s^{-1}$	$0.69 \times 10^{-6}\ s^{-1}$
k_2	$9 \times 10^{-3}\ \ell M^{-1}\ s^{-1}$	$52 \times 10^{-3}\ \ell M^{-1}\ s^{-1}$
k_3	$1 \times 10^{-4}\ \ell M^{-1}\ s^{-1}$	$0.87 \times 10^{-4}\ \ell M^{-1}\ s^{-1}$
k_{3Cl}	$0.24 \times 10^{-5}\ \ell M^{-1}\ s^{-1}$	$0.52 \times 10^{-5}\ \ell M^{-1}\ s^{-1}$
k_{4Cl}	$3.67 \times 10^{-2}\ \ell M^{-2}\ s^{-2}$	$20 \times 10^{-2}\ \ell M^{-2}\ s^{-2}$

Estimates were calculated for pH 5, 7, and 9, which is approximately the pH range of natural waters. Half-lives for chemical degradation and the chlorohydrin/glycol ratios (for sea water reactions) are summarized below:

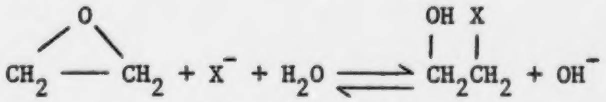
	Ethylene Oxide			Propylene Oxide		
pH	5	7	9	5	7	9
Half-life (hrs)						
Fresh water	292	338	338	159	279	279
Marine water	55.6	99	99	36.3	99	99
Ratio of $\frac{\text{chlorohydrin}}{\text{glycol}}$	4.2	2.4	2.4	3.4	4.3	4.3

While calculated degradation half-lives (and product ratios) were the same in waters of pH 7 and pH 9, half-lives were shorter at pH 5. Acid catalysis differed in effect on relative rates for chlorohydrin formation and glycol formation. So, the chlorohydrin/glycol ratio with acid catalysis was increased with ethylene oxide but was decreased with propylene oxide. The metabolic degradation reactions are not included in the above evaluation.

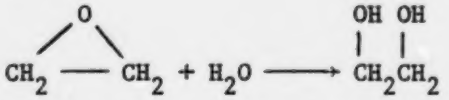
b) Degradation in Soil

There was no information available which directly evaluated reactions of the selected epoxides in soil. Epoxide degradation has been examined in cell-free extracts of a Flavobacterium sp. isolated from an alfalfa field soil (Castro and Bartinicki, 1968; Bartinicki and Castro, 1969). These studies indicated that enzymes of the Flavobacterium sp. catalyzed reaction sequences analogous to behavior described for epoxide hydrolysis.

With the cell-free Flavobacterium sp. extract, the epoxide-halohydrin reaction was reversible:



where X is bromide or chloride. The epoxide reacts with water and yields glycol:



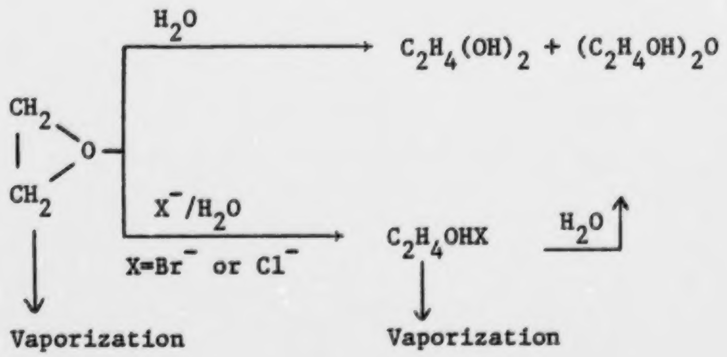
These reactions required the enzyme (cell-free extract). Relative reaction rates for enzyme catalyzed reactions of the epoxide decreased in the order $Cl^- > Br^- > H_2O$ or OH^-.

c) Degradation in Commodities and Manufactured Products

Many food commodities and manufactured products are fumigated with ethylene oxide or propylene oxide (see Section II.B.1). The fate of these epoxides and their residues is especially important in those materials, commodities, and products coming into close contact with humans, such as surgical equipment, pharmaceuticals, and food service and packaging materials (Wesley _et_ _al_., 1965; Alguire, 1973; Holmgren _et_ _al_., 1969; Gilmour, 1978).

Delineation of epoxide fate in these materials has established that they will degrade to glycol and halohydrin or evaporate. The degradation could result from chemical or enzymatic activity or from some combination of the two. The halohydrin formation requires epoxide reaction with inorganic halide. The halide could be naturally present, be added, or be derived from organic halides. Bromide ion often comes from degraded methyl bromide, which is also a fumigant (Rowlands, 1971; Lindgren _et_ _al_., 1968).

Scudamore and Heuser (1971) evaluated ethylene oxide fate for a variety of treated commodities. They examined degradation and apparent vaporization of ethylene oxide and its residues:



The losses of the ethylene oxide, ethylene chlorohydrin, and ethylene bromohydrin were measured over a one-year period. Apparent first order specific rate constants, k, were calculated for epoxide dissipation. The rate constant k combined losses from the degradation (chemical and metabolic pathways), k_D, and vaporization, k_V:

$$k = k_D + k_V$$

The glycols (ethylene and diethylene) were only determined once at either six months or a year after treatment. Table 13 (Section II.D.1) summarizes salient data for ethylene oxide residues on a variety of products. Effects considered included ethylene oxide treatment (dose and temperature during application), moisture content of the commodity, storage temperature, and storage in closed containers or in open trays. Ethylene oxide residues rapidly dissipated. While its estimated half-life was longest at 10°C in sealed containers, it never exceeded two weeks. Increasing the ethylene oxide dose had a varied effect on its loss rate. While small dose increases generally slightly decreased the loss rate, very large increases caused larger decreases in the rate of loss and sometimes caused non-linear correlations. The effect of moisture content appeared varied and relatively small. Scudamore and Heuser also monitored some commercially treated products (see Section II.E.1) and found ethylene halohydrin residues but no ethylene oxide residues. They concluded that ethylene oxide will normally dissipate from treated commodities but under some circumstances, small quantities could persist for several months.

Stijve and coworkers (1976) discussed the fate of ethylene oxide applied as a fumigant to commodities. They suggested that ethylene oxide could be retained by physical adsorption but that it would persist not more than a few weeks before volatilization or reaction with natural constituents of the commodity.

Ben-Yehoshua and coworkers (1971) examined ethylene oxide residues during the treatment of dates. Table 19 describes the ethylene oxide concentration for treatment of the fruit in a 20-liter, closed-glass container. The small ethylene oxide loss in the empty container was ascribed to apparent adsorption to container walls. The larger losses experienced with 2.1 kg of dates in the container resulted from ethylene oxide uptake by the fruit. Figure 8 describes the ethylene oxide loss in treated dates, which were left in open containers. It apparently summed losses from degradation to the chlorohydrin and glycol combined with volatilization.

The available information on fate of ethylene oxide applied to manufactured goods was not as extensive as that on its fate in commodities. All available information suggested that its behavior in manufactured products corresponds to the pathways of degradation and volatilization described above.

Alguire (1973) described losses of ethylene oxide from polystyrene creamer cups and cream cheese wrappers at ambient temperature and open to the environment. The ethylene oxide did not degrade on the polystyrene cups, and was lost solely through vaporization. More than 90% vaporized in the first day and no residual ethylene oxide remained after five days (Figure 7, Section II.D.1). Ethylene oxide loss from cream cheese wrappers primarily consisted of its conversion to ethylene glycol; no ethylene chlorohydrin was detected at any time. Ethylene oxide was completely gone by the tenth day.

Some studies have identified ethylene chlorohydrin residues in manufactured goods sterilized with ethylene oxide. These studies did not seek any information on volatilization losses. Brown (1970) identified

Table 19. Changes in Concentration of Ethylene Oxide during the Fumigation Period of Dates (From Ben-Yehoshua, *et al.*, 1971)

Ethylene Oxide Dose (ml)	Expected Concentration (%)	Kg Fruit per Container	Actual Concentration (%) after 2 h of Fumigation	Actual Concentration (%) after 22 h of Fumigation
0.4	9.3	0	8.2	7.8
0.6	14.0	2.1	7.1	2.1
0.4	9.3	2.1	5.1	1.4
0.2	4.6	2.1	2.4	0.8

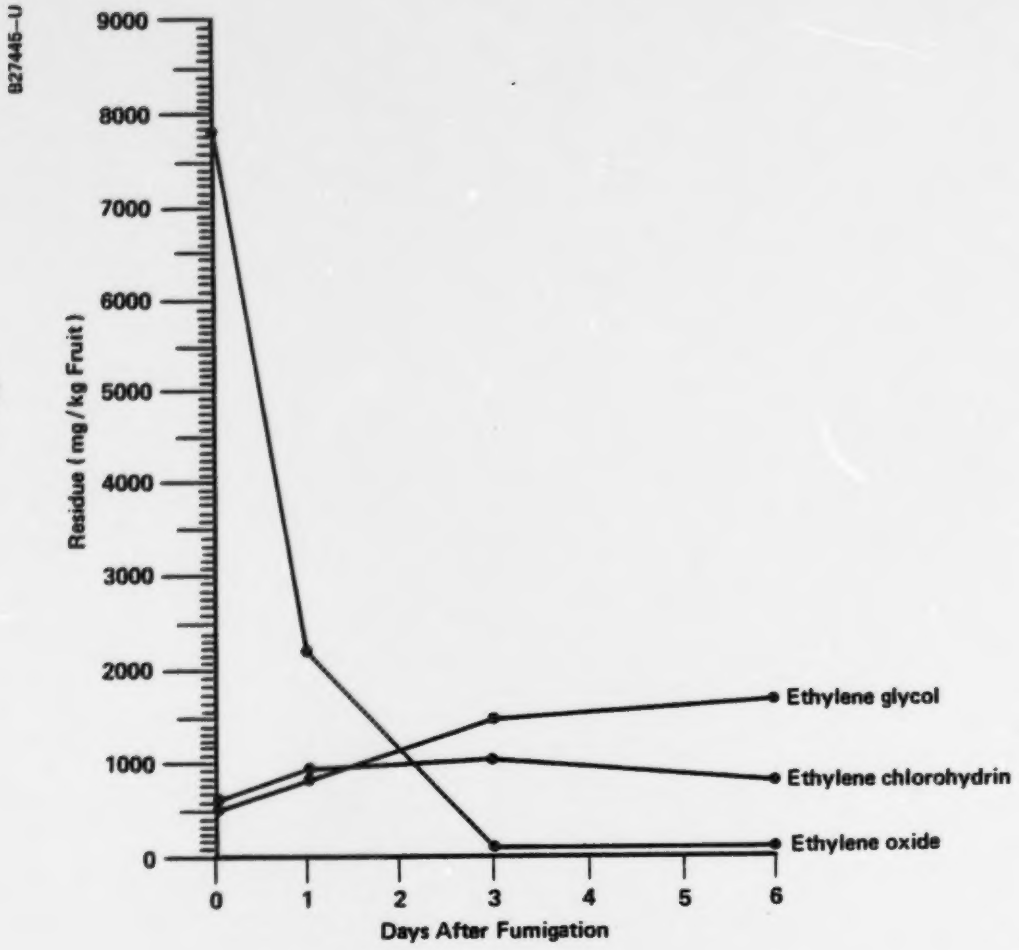


Figure 8. Changes in levels of the toxic residues in dates fumigated for 20 hrs with 16 ml ethylene oxide per kg fruit, and kept under room conditions in open jars (from Ben-Yehos hua *et al.*, 1971).

ethylene oxide and its derivatives on treated equipment made of rubber, dacron and polyvinylchloride, but did not detect chlorohydrin on polyethylene equipment. Holmgren et al. (1969) measured 0 to 1500 ppm chlorohydrin on 21 ethylene oxide treated drugs.

Although propylene oxide is also applied as a fumigant or sterilant, its fate has not been described in the same detail as ethylene oxide. Propylene chlorohydrins and propylene glycol have been identified as degradation products (Lindgren et al., 1968; Rosenkranz et al., 1975; Wesley et al., 1965). However, no information was available concerning propylene oxide dissipation.

d) Atmospheric Degradation

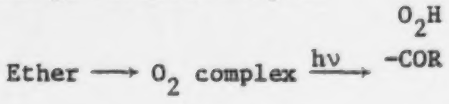
Epoxide degradation in the atmosphere can be suggested from information derived from their oxidation by free-radical pathways. No direct information on epoxide behavior in the environment was available.

Atmospheric reactivity of hydrocarbons has been characterized by their relative reaction rates with hydroxyl radicals in the gas phase (Darnall et al., 1976). Ethers as a class (epoxides are a type of ether) have been classified among the most reactive hydrocarbons. Specific information on free-radical chemistry of the epoxides was found only for liquid phase studies.

Kulevsky and coworkers (1969) examined photooxidation of ethers (including propylene oxide) in the liquid phase. They irradiated oxygenated ethers (neat solution) with a Hanovia mercury vapor lamp and measured the uptake of oxygen after one hour of irradiation. Oxygen uptake for propylene oxide was slower than uptake by other ethers by about an order of magnitude:

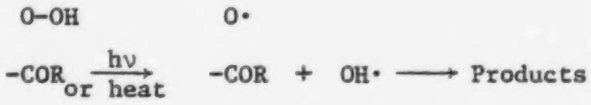
Ether	O_2 uptake after 1 hr. (mol.)
Diethyl ether	2.0×10^{-3}
Tetrahydrofuran	2.2×10^{-3}
Tetrahydropyrene	1.2×10^{-3}
Propylene oxide	0.1×10^{-3}

They investigated the products and assigned a mechanism based upon behavior of two ethers; diethyl ether and tetrahydrofuran. The initial reaction of the photochemical oxidation was assigned to hydroperoxide formation from an oxygen-ether, charge-transfer complex



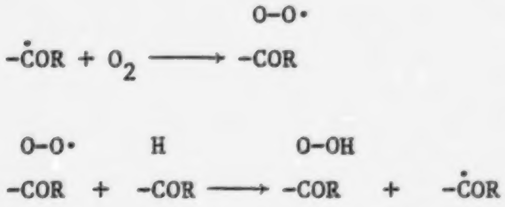
$$\text{Ether} \longrightarrow O_2\ \text{complex} \xrightarrow{h\nu} \overset{O_2H}{\text{-COR}}$$

The difference in oxygen uptake of the ethers was assigned to the basicities of the ether and its control of the equilibrium on charge-transfer complex formation. Since epoxides are less basic than analogous acyclic ethers, corresponding photolytic degradation of propylene oxide is slower. The etheral hydroperoxide subsequently cleaves and the ether further degrades by free-radical reactions.



$$\overset{O\text{-}OH}{\text{-COR}} \xrightarrow[\text{or heat}]{h\nu} \overset{O\cdot}{\text{-COR}} + OH\cdot \longrightarrow \text{Products}$$

Some free-radical chain propagation was postulated in the formation of hydroperoxide:

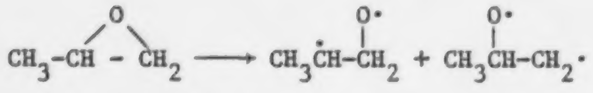


$$\text{-}\dot{C}OR + O_2 \longrightarrow \overset{O\text{-}O\cdot}{\text{-COR}}$$

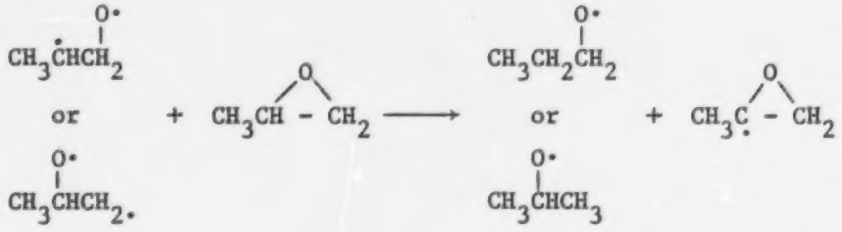
$$\overset{O\text{-}O\cdot}{\text{-COR}} + \overset{H}{\text{-COR}} \longrightarrow \overset{O\text{-}OH}{\text{-COR}} + \text{-}\dot{C}OR$$

Results of this study do not directly apply to atmospheric reactions of epoxides, since the reactions utilized high energy ultraviolet light (253.7 nm) and oxygen uptake was measured as a combination of ether-oxygen charge-transfer complex formation, of photodegradation of the complex, and of the possible radical chain propagation. However, the results do suggest that epoxides will exhibit atmospheric reactivities similar to other ethers.

Gritter and Sabatino (1964) examined ultraviolet photolysis of propylene oxide (also at 253.7 nm) in the liquid phase but in the absence of oxygen. The initial degradation was assigned to carbon-oxygen bond breaking:



The significant observation of this study concerned reaction of these initial radicals with propylene oxide:

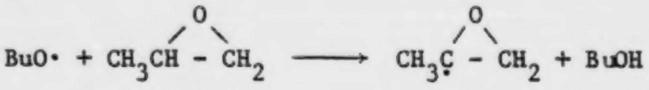


The study concluded that radical reactions with propylene oxide abstract the hydrogen at the alkyl substituted epoxide.

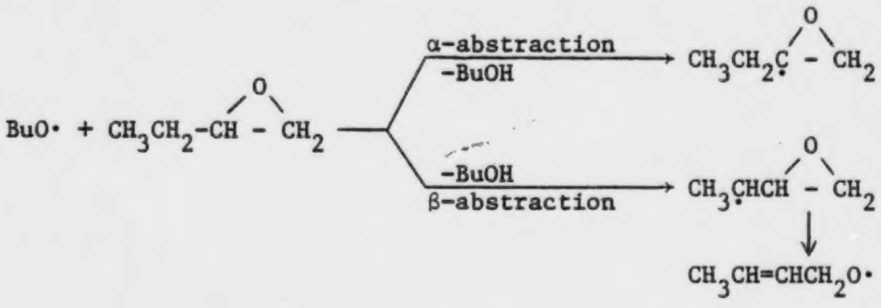
Sabatino and Gritter (1963) examined the reaction of propylene oxide and butylene oxide with t-butyl peroxide. They reacted each epoxide with t-butyl peroxide at 150°C in a deaerated glass bomb. The initial reaction in this system was peroxide decomposition to t-butoxy radicals:

$$BuOOBu \xrightarrow{heat} 2BuO\cdot$$

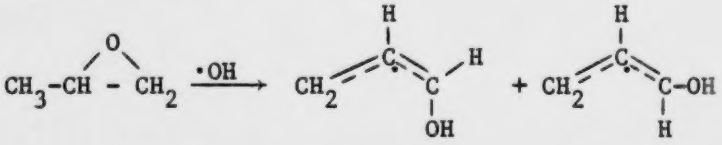
The t-butoxy radicals then abstracted hydrogen from the epoxides. Sabatino and Gritter delineated the site of hydrogen abstraction and the subsequent reaarrangement of the intermediate free-radicals by product analysis. Propylene oxide yielded only the oxiranyl radical (α-hydrogen abstraction). Allyl alcohol was the only product:



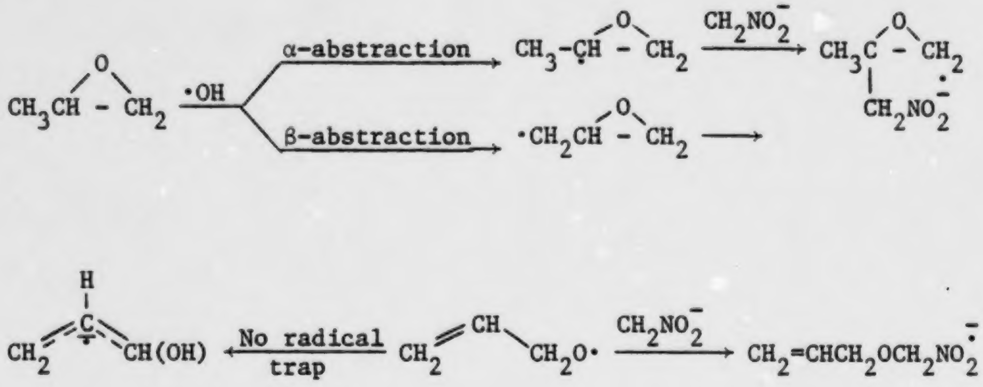
Butylene oxide yielded a mixture of 2-butanone, crotyl alcohol, and crotonaldehyde. Sabatino and Gritter assigned the first product to α-hydrogen abstraction and the latter two products to β-hydrogen abstraction:



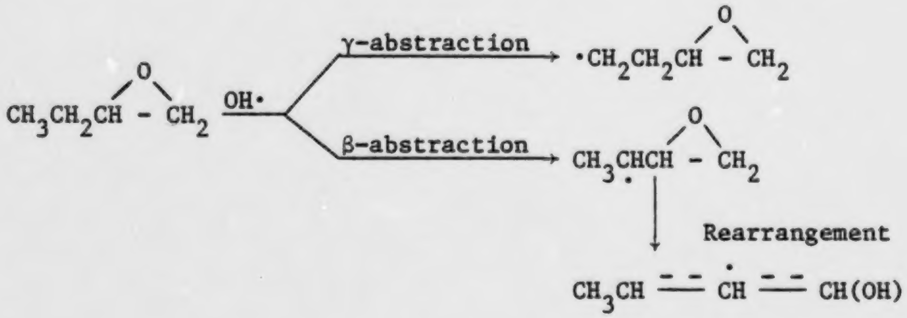
Dobbs and coworkers (1976) examined free-radicals of epoxide reactions with hydroxyl radicals by electron-spin resonance spectrometry (esr). The hydroxy radicals were generated from the titanium (III)-hydrogen peroxide system in aqueous solution. Radicals were examined with nitromethane as a radical trap and without any radical trap. The esr for hydroxide radical-propylene oxide system in the absence of nitromethane indicated that only products of β-hydrogen atom abstraction were generated. They concluded that the propylene oxide yielded 1-hydroxyallyl radical, which was present as two geometric isomers:



In the presence of nitromethane they observed evidence for the formation of the propylene oxide α-radical as well as the β-radical:

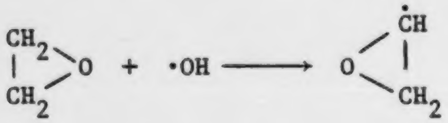


Dobbs and coworkers (1976) only examined the esr of radicals generated from butylene oxide in the absence of the radical trap. Butylene oxide yielded radicals from apparent abstraction of β-hydrogen and γ-hydrogen:

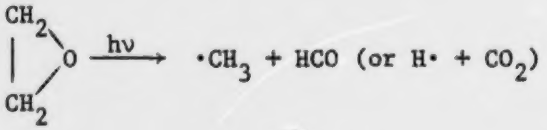


They identified the 3-hydroxy-1-methylallyl radical, which is an apparent rearrangement product of the β-radical and the unrearranged γ-radical.

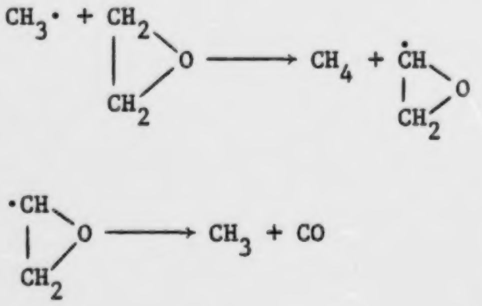
Although no direct information was available on the atmospheric reactions of ethylene oxide, a description of its probable degradation pathway can be constructed from studies on its photochemistry and on its reaction with oxide radicals. Dobbs and coworkers (1971) examined the latter. They generated oxiranyl radical using hydroxyl radicals (generated from Ti(III) ion-hydrogen peroxide) or t-butoxyl radicals (from di-t-butyl peroxide) in aqueous solution. The oxide radicals abstracted hydrogen and yielded oxiranyl radical:



This oxiranyl radical was also generated by photochemical reaction (Gomer and Noyes, 1950; Cvetanovic, 1955). Ethylene oxide yielded primarily CO, H_2 and CH_4 when it was irradiated in the gas phase with mercury added as a photosensitizer. The primary irradiation process assigned was:



The ethylene oxide was subsequently degraded by a chain mechanism:



In conclusion, the epoxides evidently are degraded in the atmosphere by free-radical processes. Their reactivity with hydroxyl radical has not been documented, but the evidence at hand indicates that the epoxides have a similar reactivity to other ethers. They are expected to degrade rapidly in the environment.

3. Persistence, Bioaccumulation and Food-Chain Accumulation

Epoxides will not persist in the environment nor will they accumulate in the food chain. The epoxides degrade through chemical and metabolic pathways. Bioaccumulation potential has been correlated with water solubility (Freed _et_ _al_., 1977). The high water solubilities of the selected epoxides characterize them as incapable of bioaccumulating.

E. Detection in Environmental and Biological Samples

1. Monitoring

Ambient monitoring has portrayed the selected epoxides as minor contaminants of environmental or biological samples. The epoxides produced and consumed in the greatest amounts are ethylene oxide and propylene oxide. Although these two epoxides appear seldom identified in monitoring studies, their principal degradation products (glycols and halohydrins) have been identified (see Section II.D).

No monitoring data was available for epoxides in biological tissues except for some tissue distribution studies (see Section III C.1.a). Since the epoxides are reactive alkylating agents, it is reasonable to expect such results (Anderson, 1971).

Shackelford and Keith (1976) listed one monitoring observation for propylene oxide in water. It was observed in the effluent from a chemical plant in Bandenburg, Kentucky. No other epoxide observation was reported. Shackelford and Keith also noted observations of ethylene and propylene halohydrins, but they might be industrial wastes rather than residues from the epoxides.

Several studies have examined the residues of ethylene oxide and propylene oxide applied to commodities and manufactured goods as fumigants and disinfectants. The information on residues in commercial products is discussed here. Another portion of this report (Section II.D) describes investigations on the fate of these same epoxides. The present section differs in that the information concerns residues in actual commercial products.

Scudamore and Heuser (1971) evaluated ethylene oxide and its metabolites in commercially treated products, and also did some fate studies (discussed in Section II.D). While they never detected ethylene oxide in commercial products, they did find ethylene chlorohydrin residues ranging from 10 to 70 ppm.

Lindgren et al. (1968) reviewed studies on residues from ethylene oxide and propylene oxide treatment; most of which were fate studies rather than ambient monitoring studies. Their review suggested that residual epoxide could be present in commercial products.

Ethylene oxide is a common sterilant for surgical equipment (see Section II.B.1). Its fate in plastic and rubber surgical equipment parallels its behavior in commodities. Brown (1970) monitored residues on various hospital equipment sterilized with ethylene oxide. Table 20 summarizes results of the study. Brown did observe ethylene oxide in three samples, one of which had received treatment about 80 days previously.

No information was available on selected epoxide monitoring in the ambient atmosphere.

2. Analytics

Gas chromatography (GC) is currently the best available method for epoxide analysis. The GC contains an analytical column to separate components of the sample and a detector to quantify each component as it leaves the

Table 20. Summary of Ethylene Oxide and Chlorohydrin Determinations on a Variety of Surgical Equipment (From Brown, 1970)

Sample	Material	Time from Sterilization to Extraction, Days	Extraction Time	Ethylene Oxide, ppm	Ethylene Chloro-hydrin, ppm
Heart catheters (Gensini)	Woven Dacron	Unknown	3 days	ND[a]	2.0
Heart catheters (Gensini)	Woven Dacron	Unknown	3 days	ND	3.0
Heart catheters (Cournand)	Woven Dacron	Unknown	3 days	ND	ND
Heart catheters (Gensini)	Woven Dacron	1	3 days	ND	27
Tubing	Polyethylene	Unknown	2 days	ND	ND
Suction catheters	Polyethylene	Unknown	2.5 days	ND	ND
Tubing	Polyethylene	Unknown	3 days	ND	ND
Tubing	Polyethylene	Unknown	2 days	ND	ND
IV catheter unit	Teflon	Unknown	19 hr	ND	ND
Sterile gloves	Plastic	Unknown	2.5 days	ND	ND
Transfusion unit	PVC	ca 50	1 hr	-	1.5
Transfusion unit	PVC	ca 80	1 hr	1.8	ND
Foley catheter	Rubber	Unknown	20 hr	ND	ND
Surgeons' gloves	Rubber	Unknown	28 hr	ND	ND
Surgeons' gloves	Rubber	Unknown	28 hr	ND	ND
Surgeons' gloves	Rubber	1	3 days	2.4	1.9
Surgeons' gloves	Rubber	1	3 days	3.1	1.9
Penrose tubing	Rubber	1	1 day	None	7.1
Surgeons' gloves[b]	Rubber	2	1 hr	-	13
Surgeons' gloves[b]	Rubber	8	1 hr	-	11
Surgeons' gloves[b]	Rubber	35	1 day	-	3.3

[a] None detected.

[b] Same lot number.

column. The analysis requires that the sample is injected into the column in a suitable solvent or as a gas. The sample preparation is critical to analysis.

The state-of-the-art in air sampling utilizes solid sorbents. Samples can subsequently desorb by solvent or by thermal means. Critical factors in the method are the sorbent's capacity to retain the epoxide during the collection and the complete desorption of epoxide.

Pellizzari and coworkers (1976) evaluated Tenax GC and other sorbents for sampling atmospheric propylene oxide. Table 21 compares the breakthrough volumes for several sorbents. The effect of humidity on the breakthrough volume was tested for Tenax GC. Breakthrough volume increased from 4.0 to 4.5 liters/g when humidity was increased from 41% to 92%. Pellizzari and coworkers (1976) also examined the effect of storage time on the recovery of diepoxybutane (300 ng) loaded onto Tenax GC cartridges. They desorbed thermally and analyzed by GC. When analysis was immediate, recovery was 100%. After the loaded cartridge was stored one week, the recovery dropped to 76%. Combined transport (six days) and storage yielded recoveries of 75% and 64% after one and two weeks, respectively.

The National Institute for Occupational Safety and Health (NIOSH) has published standard procedures for ethylene oxide and propylene oxide collection in air (NIOSH, 1976). Their procedure calls for the sampling of 5 liters of air through glass tubes packed with activated coconut shell charcoal. For ethylene oxide two tubes mounted in series are used; the front and back-up tubes contain 400 mg and 200 mg, respectively, of charcoal. For propylene oxide NIOSH recommends a commercially available 150 mg tube which contains 100 mg charcoal in the front section and 50 mg in the back-up section.

Table 21. Breakthrough Volume for Propylene Oxide with Several Sorbents. (From Pellizzari *et al.*, 1976)

Sorbent	Breakthrough Volume (ℓ/g)
PBL Carbon	36
PCB Carbon	40
SAL9190	40
MI808	24
Tenax GC (35/60)[a]	4
Porapak Q (100/120)	4
Chromosorb 101 (60/80)	4
Chromosorb 102 (60/80)	8
Chromosorb 104 (60/80)	>36

[a] Mesh size.

The front and back-up sections are individually measured for epoxide. If the back-up portion contains more than 25% of the epoxide, the analysis is not considered valid. The method suggests desorbing the epoxide with carbon disulfide. The required solvent amounts are 2.0 and 0.5 ml for ethylene oxide and propylene oxide, respectively. Aliquots of the desorbed solutions are then analyzed by GC with flame ionization detection. NIOSH conducted tests on the analytical parameters. Ethylene oxide was examined at concentrations from 41 to 176 mg/cu m (0.23 - 0.98 ppm); precision (CVT) was 0.103 (or standard deviation of 9.3 mg/cu m) and accuracy was 0.9% lower than the "true" value. NIOSH recommended sample concentrations of 20 to 270 mg/cu m for this method. Propylene oxide samples were evaluated at concentrations from 121 to 482 mg/cu m (50 to 200 ppm); precision $(\overline{CV}_T)$ was 0.085 (or standard deviation of 20 mg/cu m) and accuracy was 5.6% below "true" value. NIOSH recommended sample concentrations of 25 to 720 mg/cu m with this method.

Romano and Renner (1975) described the results of a six laboratory intercomparison of three methods for sampling ethylene oxide in surgical equipment, the study was administered through the Z79 Subcommittee on Ethylene Oxide Sterilization of the Association for Advancement of Medical Instrumentation. The three sampling methods were vacuum extraction with sample freezeout; headspace analysis; and acetone extraction. The vacuum-freezeout technique required distillation of volatiles from the sample and freezing them in a cold trap. The sample was then vaporized and an aliquot removed with a vacuum syringe for GC analysis. Romano and Renner reported that the method requires greater time and equipment than the other techniques and is subject to errors from equipment leaks. Its advantages are that it is the most sensitive, and since the sample injected into the GC is a vapor, column life is long. Acetone extraction consists of partitioning the epoxide between the sample and the acetone solvent. Its advantage is its simplicity. Its disadvantages include its inability to quantitatively extract epoxide, problems from impurities in the solvent and extraction of other compounds from the plastics, the reduced lifetime of columns because of these impurities, and low sensitivity. In headspace analysis the sample is placed into a vial which is equipped with a septum for gas withdrawl by syringe. The epoxide partitions between the sample and headspace gases. The advantages of this technique include its ease of performance, speed, sensitivity and relatively long column life. Its disadvantage is that leaks in septa, vial caps, etc., can yield low measurements.

Romano and coworkers (1973) reported that the headspace technique has a lower limit of 0.1 ppm and that the technique can be automated. Romano and Renner (1975) evaluated results for the three methods at six laboratories by analysis of variance. Among overall methods there were no significant differences. However, slight differences between laboratories were detected.

Ben-Yehoshua and coworkers (1971) extracted fruit pulp by blending it with 50 ml of analytical grade acetone for 30 seconds, filtering the homogenate to clarity. The samples were then stored at -10°C in bottles with self-sealing stoppers. Measurements (by GC) of added ethylene oxide and its residues were accurate to ±5%.

Scudamore and Heuser (1971) extracted wheat flour and other commodities including coconut, sultanas, lentils, and ground nuts with 5:1 (v/v) analytical grade acetone-water. The extraction used as little as 3 ml solvent/g sample. A contact time of 24 hours was sufficient to yield ethylene oxide recoveries (by GC) of 95% or better.

Pfeilsticker and coworkers (1975) extracted 10 g grain (not comminuted) with 5 ml of methanol using continuous agitation for 24 hours. Recovery of ethylene oxide (25 ppm) was 73% and standard deviation (with GC analysis) was 1.70 ppm.

Brown (1970) sampled and analyzed surgical materials (plastic and rubber) for ethylene oxide residues by means of a three column chromatography system. Brown could separate ethylene oxide and its degradation product, ethylene chlorohydrin. Samples were extracted with p-xylene (3 days contact) or co-sweep distillation. The three column system consisted of: I. Fluorosil, II. acid-celite, and III. Fluorosil. The p-xylene solution was passed through Column I; ethylene chlorohydrin remained fixed in the column and ethylene oxide passed through. The ethylene oxide solution was passed through the acid-celite column which converted it to ethylene chlorohydrin. Column III retained the ethylene chlorohydrin which was subsequently eluted with petroleum ether. The sample was concentrated with a Kuderna-Danish apparatus, then analyzed by GC. Brown (1970) reported values as low as 1.8 ppm, but accuracy, precision, and minimum detection limit were not described.

Thus far, GC for the epoxides has only used flame-ionization or thermal conductivity detection. Neither detection system is selective so the epoxides must be separated from all interferences and the choice of analytical column depends on potential interferences. Columns for epoxide analysis have included uncoated Poropak Q, QS and R, and Chromosorb 102 (Taylor, 1977a,b; Ben-Yehoshua and Krinsky, 1968; Steinberg, 1977) and a variety of coated columns. The most common liquid phases appear to be SE-30, Carbowax 20M, and polypropylene glycol (Ben-Yehoshua and Krinsky, 1968; Casteignau and Halary, 1972; Steinberg, 1977; Hughes *et al.*, 1959). The GC methods in current use appear capable of epoxide analysis at the ppm level.

Complex mixtures of hydrocarbons and other organic substrate could interfere with epoxide elution through a single GC column. When Hughes and coworkers (1959) examined products from gasoline combustion in automobile engines, they utilized a three-stage GC system to overcome the lack of sufficient separation capacity of any single column. The three stages were: (1) glycerol on firebrick, (2) PEG400 on firebrick, and (3) DC550 silicone oil and stearic acid on firebrick. Analysis for ethylene oxide and propylene oxide required sample elution through all three to separate them from interferences; for example, propionaldehyde interference with propylene oxide and acetaldehyde interference with ethylene oxide.

Other analytical methods include alternative forms of chromatography and various wet chemical techniques. The other chromatographic methods such as thin-layer, gel permeation, and paper, are only qualitative. Epoxides can be analyzed by ring opening with specific reagents and subsequent analysis for the reagent or one of its products (Dobinson _et_ _al_., 1969). Mishmash and Meloan (1972) reported perhaps the most recent use of this approach. Butylene oxide was hydrolyzed to its glycol, then the glycol was oxidized with periodic acid. Residual oxidant was analyzed by adding CdI_2-starch and then measuring the starch-I_3 complex concentration at 590 nm. They claimed a detection limit in the nmole range.

III. HEALTH AND ENVIRONMENTAL EFFECTS

A. Humans

1. Occupational Exposure Studies and Poisoning Incidents

Ethylene oxide toxicity following acute vapor exposure has been reviewed in a number of sources (Hollingsworth et al., 1956; Curme and Johnston, 1952). Three cases of systemic poisoning were cited by von Oettingen (1939) in which headache, vomiting, dyspnea, diarrhea, and lymphocytosis were observed. Sexton and Henson (1949) describe symptoms in three chemical plant workers drenched with 1% aqueous ethylene oxide solution. All three workers developed marked nausea and profuse vomiting after a delay of several hours. Exposed skin areas developed large vesiculated blisters without significant erythema. The two workers who had complete blood counts taken following exposure showed a transient elevation of the total leukocyte count (12,000-16,000/cubic millimeter). In a case of illness observed in six workers exposed to carboxide (ethylene oxide/carbon dioxide) gas while working in a ship compartment, Blackwood and Erskine (1938) reported symptoms of headache, nausea, vomiting, and respiratory irritation. Similar effects were reported in 10 women workers overcome by ethylene oxide in a California food plant (Anon., 1947). Thiess (1963) reported that high concentrations of ethylene oxide for brief periods produced bronchitis, pulmonary edema, and emphysema in industrial accidents.

The dermatological effects of ethylene oxide contact were reviewed by Taylor (1977c). Pure ethylene oxide evaporates rapidly from the skin and produces a freezing effect. Burns ranging from first degree through third degree severity have been seen after ethylene oxide exposure. Phillips and Kaye (1949) reported foot burns from rubber boots sterilized with ethylene oxide. Royce and Moore (1955) recorded burns after use of rubber gloves exposed to ethylene oxide. Biro and coworkers (1974) described a hospital incident in which 19 women suffered from burns received from surgical gowns and drapes sterilized with ethylene oxide. Joyner (1964) reported burns experienced by workers in an ethylene oxide plant in a two-year retrospective study of medical records.

In a study of chemical burns of the human cornea, McLaughlin (1946) reported an acute case induced by ethylene oxide and three cases resulting from propylene oxide exposure. All of the workers showed rapid healing in the 48 hours following a corneal denudement procedure. Thiess (1963) described two cases of accidental eye injury with ethylene oxide. A nurse was exposed to a direct blast of ethylene oxide from a sterilizer cartridge, and developed an epithelial keratitis of the cornea within three hours. Within 24 hours the eye was entirely normal. The second case involved a patient who received a squirt of liquid ethylene oxide (concentration not stated) in the eye. After extensive washing, irritation of the conjunctivae followed and persisted for about one day.

Clinical reports of hemolysis following usage of ethylene oxide sterilized plastic tubings have been made by Hirose and coworkers (1953) and Clarke and coworkers (1966). Ethylene oxide, rather than a chemical reaction product, was implicated since this type of effect can be prevented by extensive aeration of ethylene oxide sterilized plastic devices.

Anaphylactic reactions have been observed in patients using ethylene oxide sterilized plastic tubing for hemodialysis (Poothullil _et_ _al_., 1975) or cardiac catheterization (Pessayre and Trevoux, 1978). These symptoms included uticaria, breathlessness, and hypotension. In a followup study on a patient apparently sensitized to contact with hemodialysis tubing, Dolovich and Bell (1978) illustrated that this patient showed a positive skin test response to ethylene oxide-serum albumin conjugate and produced in vitro histamine release to this antigen. This response indicates that a specific IgE antibody to ethylene oxide had been induced in this patient..

Propylene oxide shares many of the toxic properties of ethylene oxide with injury to the eyes and skin having been reported (Hine and Rowe, 1973). Based on animal studies, Jacobsen and coworkers (1956) have estimated that propylene oxide is approximately two to three times less toxic than ethylene oxide.

2. Controlled Human Studies

In an investigation of the effects of ethylene oxide on human volunteers, Greaves-Walker and Greeson (1932) observed that ethylene oxide at approximately 2200 ppm was slightly irritating to four subjects. At a five-fold higher concentration the compound had a definite irritating effect on nasal mucosa within about 10 seconds. Liquid ethylene oxide applied to the skin boiled off rapidly without producing irritation or erythema. Similarly, ethylene oxide vapor in a test tube held inverted on the skin of volunteers for 15 minutes produced no visible effects.

Sexton and Henson (1950) tested human subjects for dermal reactions to aqueous ethylene oxide solutions. The most severe development of characteristic bullae (blisters) was with a 50% ethylene oxide solution. Three of eight volunteers showed signs of delayed skin sensitization.

3. Epidemiology

An investigation of health incidents in Veterans Administration hospitals (162 hospitals and 7 outpatient clinics) using ethylene oxide sterilization equipment indicated that, in an 8-year period, several employees suffered watering eyes, nausea, and skin irritation (NIOSH, 1977). A followup study is in progress to determine possible sequelae to these incidents. Jensen (1977, unpublished) reported that three workers using ethylene oxide sterilizers were hospitalized for neuropathy of the lower limbs. Followup indicated these effects were reversible. Gross et al. (1979) also reported finding peripheral neuropathy in three workers and acute encepholopathy in an additional operator of a leaking ethylene oxide sterilizer. One worker removed from exposure showed evidence of recovery.

Joyner (1964) conducted a retrospective morbidity study of 37 male employees at an ethylene oxide production plant. These 29-to-56-year old male workers were exposed to 5 to 10 ppm for a period of 5 to 16 years. Controls consisted of operators assigned to other production units, with no indication of types of chemical exposure in these units. Three ethylene oxide operators refused to participate in the study, but their previous medical records were used in the overall evaluation. Workers exposed to ethylene oxide who had left the plant were not included. No significant increase in health problems relative to controls was found. This evaluation should identify major toxic effects of ethylene oxide, but the size of the group studied, the exposure duration, and the duration of observation preclude any evaluation of more subtle toxic or carcinogenic responses.

Hematological and chromosomal studies were performed on all factory workers (male) in a Swedish ethylene oxide production factory during 1960 and 1961 (Ehrenberg and Hallstrom, 1967). Workers were classified in one of the following five groups: 66 persons not in contact with ethylene oxide, 86 persons in intermittent contact, 54 persons with some extended contact, 37 persons in permanent contact, and 8 persons exposed to high accidental concentrations of ethylene oxide. The comparison of exposed and control groups indicated certain differences. Certain cellular abnormalities, such as three cases of anisocytosis and one case of leukemia, were observed in the exposed group. Lower hemoglobin values were found in the exposed group. The high ethylene oxide (accident) exposure group showed higher numbers of chromosomal aberrations. Statistical evaluation of these findings was not available for examination. A followup of this study is planned.

Recently, a study of 230 Swedish factory workers exposed to 20 ± 10 ppm (TWA) ethylene oxide over a nine year period was reported (Hogsted et al., 1979). Three cases of leukemia were found in the 236 workers compared with an expected 0.2 case incidence in this population. The gas used for sterilization of hospital products was an equal mixture of ethylene oxide and methyl formate. Leakage from gas-sterilized storage boxes located in a working-hall area could have produced local levels of 150 ppm. Monitoring of ethylene oxide levels was done only recently, and correlation with levels several years previously may be very poor. Methyl formate may have contributed to the effects seen, but it is less volatile than ethylene oxide and less reactive chemically. Latency time for the three leukemia cases was four years, six years, and eight years, respectively.

Yakubova and coworkers (1976) reported that pregnant workers in ethylene oxide production facilities were prone to miscarriages and toxicosis in the second half of pregnancy. Levels of exposure and quantitation of effects were not available for analysis.

B. Reported Effects on Nonhuman Animals from Industrial Release, Spills, and Accidents

No data are available concerning these types of effects from the epoxides under consideration.

C. Experimental Studies on Animals

1. Toxicity and Effects on Mammals

a) Metabolism

Inhalation studies with radioactively labelled [1,2 ^{3}H] ethylene oxide were carried out by Ehrenberg et al. (1974). Following exposure of mice to 1.1 ppm labelled ethylene oxide for 75 minutes, high levels of radioactivity were measured in the lungs, kidney, liver, testis, and moderate levels in the brain and spleen. Approximately 80% of the radioactivity absorbed was excreted in the urine within 48 hours indicating rapid urinary elimination. The only urinary metabolite characterized was 1-hydroxyethyl guanine which comprised a minor amount (.007%) of the total urinary radioactivity. Tissue proteins isolated from lung, liver, kidney, spleen, and testis were alkylated in vivo by ethylene oxide, as was a nucleic acid fraction of the kidneys. Thus, ethylene oxide distributes and reacts extensively throughout the body. A biological half-life for ethylene oxide following i.p. injection was determined as nine minutes.

Appelgren and coworkers (1977) carried out whole body autoradiography on mice that were injected i.v. with radioactive [^{14}C] ethylene oxide (label position unspecified). Preliminary inhalation studies with labelled ethylene oxide showed a similar tissue distribution of the compound as that seen following i.v. injection, except for a high initial labelling of respiratory mucosa (data not shown). Concentrations of radioactivity two to three times those seen in the blood were observed after two minutes in the liver, kidney, and pancreas. Tissue labelling after 20 minutes to four hours showed high levels in the liver, kidney, lung, intestinal mucosa, epididymis, cerebellum, and testes. Twenty-four hours after injection, radioactivity was still found in the liver, intestinal mucosa, epididymis, cerebellum, bronchi, and bone marrow. Since these observations were made on autoradiographs quantitative results were not reported.

b) Acute Toxicity

Ethylene Oxide - The acute toxicity of ethylene oxide is summarized in Table 22. Exposure to concentrated ethylene oxide produces systemic poisoning with symptoms of salivation, nausea, vomiting, diarrhea, delayed paralysis of the hind quarters, convulsion, and death (Hine and Rowe, 1973). Sexton and Henson (1949) have noted symptoms of respiratory irritation, nausea, vomiting, incoordination, and cardiac arrhythmia. Studies on rabbits administered lethal doses of ethylene oxide intravenously indicated that death followed convulsive seizures. Pathology revealed congestion of all organs (Greaves-Walker and Greeson, 1932). Inhalation studies at a lethal concentration (∿11,100 ppm) in mice, rats, and guinea pigs showed pathological congestion of the lungs and, in some cases, an acute pneumonic condition. Guinea pigs exposed to lethal inhalation levels (3,000 to 50,000 ppm) showed acute congestion of the lungs, hyperemia of the liver and kidneys, and gray discoloration of the liver (Waite et al., 1930). Animals that showed delayed deaths had developed lobar and lobular pneumonia. Hollingsworth and coworkers (1956) detailed symptoms seen after lethal inhalation exposure to ethylene oxide (250 to 4,000 ppm) in mice, rats, dogs, guinea pigs, and rabbits. Animals surviving initial exposures showed subsequent bronchitis and loss of appetite. Delayed effects of apathy, dyspnea, vomiting, hind leg paralysis, severe respiratory distress, periodic convulsions, and death were observed. Pathology showed emphysema of the lungs, congestion and fatty degeneration of the liver, cloudy swelling of kidney tubules, and congestion of the spleen and

Table 22. Acute Toxicity of Ethylene Oxide

Route	Species	Sex	Strain	LD_{50}	Reference
Oral	rat	M	Wistar	330 mg/kg	Smyth et al. (1941)
Oral	guinea pig	M,F		270 mg/kg	Smyth et al. (1941)
Ihl.	rat	M,F	Sherman	4000 ppm/4 hrs.*	Carpenter et al. (1949)
Ihl.	guinea pig			7000 ppm/2 1/2 hrs.**	Waite et al. (1930)
Ihl.	mouse	F		835 ppm/4 hrs.*	Jacobsen et al. (1956)
Ihl.	dog	M		960 ppm/4 hrs.*	Jacobsen et al. (1956)
I.v.	dog			125 mg/kg	Patty (1973)
I.p.	mouse	M,F		178 mg/kg	Bruch (1973)
I.p.	rabbit	M,F		251 mg/kg	Woodward and Woodward (1971)
I.v.	rabbit	M,F		178 mg/kg	Woodward and Woodward (1971)
S.c.	rabbit	M,F		200 mg/kg	Woodward and Woodward (1971)
Oral	rabbit	M,F		631 mg/kg	Woodward and Woodward (1971)
I.v.	rat	M		355 mg/kg	Bruch (1973)
I.p.	rat	M,F		178 mg/kg	Bruch (1973)

*LC_{50}

**LC_{low}

brain. In general, rats, guinea pigs, rabbits, cats, and dogs showed no deaths following up to 8 hours of exposure to 250-280 ppm ethylene oxide (Hine and Rowe, 1973).

Ethylene oxide in 10% and 50% aqueous solutions produced hyperemia and edema in shaved rabbit skin when applied through cotton pads for one to sixty minutes (Hollingsworth et al., 1956). Bruch (1973) studied the dermal irritation properties of 2% to 10% aqueous ethylene oxide solutions in guinea pigs and rabbits. Subcutaneous injection in the guinea pig resulted in ecchymoses and skin thickening, while intradermal injection and topical application in the rabbit resulted in mild irritation.

McDonald and coworkers (1977) studied the ocular effects of varied concentrations of ethylene oxide in saline applied repeatedly over a six-hour period to the eyes of rabbits. They observed a dose-dependent increase in congestion, swelling, discharge, iritis, and corneal cloudiness indicating the irritating effect of ethylene oxide on mucous membranes and corneal epithelium. The maximum nondamaging concentration for this time period was 0.1% ethylene oxide. In another study of ocular irritation in rabbit eyes, Woodward and Woodward (1971) found slight irritation following a single application of 10% aqueous ethylene oxide (duration of exposure unknown). A no-effect concentration of 2.1% ethylene oxide was determined. The higher values determined in this study are probably the results of a different mode of application and, thus, different duration of exposure.

Zamlauski and Cohen (1976) have reported that infusion of ethylene oxide in the rat at blood levels of 0.45 to 4.5 mg/ml produced a significant decrease ($\sim$30%) in glomerular filtration rate, indicating ethylene oxide effects on kidney function.

Propylene Oxide - Acute toxicity resulting from exposure to propylene oxide is shown in Table 23. Rowe and coworkers (1956) determined that oral feeding (intubation) of 1000 mg/kg aqueous propylene oxide killed all rats tested, while a single oral dose of 300 mg/kg allowed the survival of all animals fed. Rats and guinea pigs exposed to high vapor concentrations of propylene oxide (4,000 to 16,000 ppm) developed persistent lung irritation. Secondary respiratory infections in these animals often led to death. Propylene oxide was shown to have a relatively weak anesthetic effect. Rats were able to tolerate exposure to concentrations of 4000 ppm for one half hour or 2000 ppm for two hours without organic damage. Application of undiluted or strong aqueous (10% to 20%) propylene oxide solutions to the skin of rabbits for six minutes or longer produced hyperemia and edema. Undiluted propylene oxide produced severe burns when applied directly to the eyes of rabbits (Carpenter and Smyth, 1946).

Inhalation studies with propylene oxide vapor conducted by Weil and coworkers (1963) showed that exposure of rats to concentrated vapor caused the death of all animals in five minutes. A concentration of 4000 ppm propylene oxide killed four of six rats exposed for a period of four hours.

Jacobsen and coworkers (1956) conducted inhalation studies comparing the toxicity of ethylene oxide and propylene oxide. Symptoms produced in rats, mice, and dogs following acute exposure to propylene oxide vapor for four hours paralleled those seen following ethylene oxide administration - lacrimation, salivation, nasal discharge, gasping, convulsions, vomiting (in the dogs), and death. Pathologic examination of the dogs showed damage to respiratory epithelium, vascular congestion, and edema of the lungs. Based on the relative LC_{50} values calculated for these species, the authors

Table 23. Acute Toxicity of Propylene Oxide

Route	Species	Sex	Strain	LD_{50}	Reference
Oral	rat	M	Wistar	1140 mg/kg	Smyth *et al*. (1941)
Oral	guinea pig	M,F		690 mg/kg	Smyth *et al*. (1941)
Dermal	rabbit			~1730 mg/kg	Smyth and Carpenter (1948)
Ihl.	rat		Sherman	<4000 ppm/4 hrs.*	Smyth and Carpenter (1948)
Ihl.	rat	M		4000 ppm/4 hrs.*	Jacobsen *et al*. (1956)
Ihl.	mouse	F		1740 ppm/4 hrs.*	Jacobsen *et al*. (1956)
Ihl.	guinea pig	F		4000 ppm/4 hrs.**	Rowe *et al*. (1956)
Ihl.	dog	M	Beagle	2000 ppm/4 hrs.**	Jacobsen *et al*. (1956)

*LC_{50}

**LC_{low}

concluded that propylene oxide was one-half to one-third as toxic as ethylene oxide.

Butylene Oxide - Acute toxicity data for butylene oxide are summarized in Table 24. In a series of toxicological studies Smyth and coworkers (1962) determined that the LD_{50} value for oral administration of butylene oxide to rats was similar to the value determined for propylene oxide in the same animals (∿1100 mg/kg). Dermal application to shaved rabbit skin also showed the comparable toxicity of butylene oxide and propylene oxide. Exposure of rats to 4000 ppm concentration of butylene oxide vapor for four hours by inhalation resulted in the death of one of six test animals. Dermal irritation to shaved rabbit skin using a one-day uncovered application was found to be insignificant. However, it is not clear if concentrations other than pure material were tested. Corneal injury produced in rabbit eyes was slightly less than that produced by propylene oxide in the same animals, indicating that concentrated butylene oxide solutions could induce corneal burns with sufficient duration of exposure. Exposure to concentrated butylene oxide vapor caused the death of all rats in 12 minutes; animals exposed six minutes showed some deaths from secondary pneumonia (Hine and Rowe, 1973).

Diepoxybutane - The acute toxicity produced by diepoxybutane is summarized in Table 25. Determination of the oral LD_{50} level in rats by Weil and coworkers (1963) indicates that diepoxybutane is more toxic by this route than ethylene oxide. The concentrated compound is well absorbed when applied to the shaved skin of rabbits, showing an LD_{50} value of 39 mg/kg. Exposure of rats to a concentrated diepoxybutane vapor resulted in the death of all test animals in 15 minutes. Diepoxybutane vapor at 125 ppm killed one out of five rats in a four-hour period. The compound is quite irritating to rabbit skin and produces pronounced corneal injury to the eyes of rabbits

Table 24. Acute Toxicity of Butylene Oxide

Route	Species	Sex	Strain	LD_{50}	Reference
Oral	rat	M	Wistar	LD_{low} 1170 mg/kg	Smyth et al. (1962)
Ihl.	rat	M,F	Wistar	4000 ppm/4 hrs.*	Smyth et al. (1962)
Dermal	rabbit	M	New Zealand	1740 mg/kg	Smyth et al. (1962)

*LC_{low}

Table 25. Acute Toxicity of Diepoxybutane

Form	Route	Species	Sex	Strain	LD_{50}	Reference
d,*l*	oral	rat	M,F	Wistar	780 mg/kg	Smyth *et al*. (1954)
d,*l*	dermal	rabbit	M	New Zealand	970 mg/kg	Smyth *et al*. (1954)
d,*l*	i.p.	mouse			25 mg/kg	Merck (1968)
l	i.p.	mouse		A/J	16 mg/kg	Shimkin *et al*. (1966)
d,*l*	ihl.	rat			125 ppm/4 hrs.*	Weil *et al*. (1963)
d,*l*	oral	rat			97 mg/kg	Weil *et al*. (1963)
d,*l*	dermal	rabbit			39 mg/kg	Weil *et al*. (1963)

*LC_{low}

(severe burns from 0.5 ml of a 1% solution). Intracutaneous injection of diepoxybutane produced delayed hypersensitivity in all eighteen guinea pigs tested.

c) Subacute Toxicity

Ethylene Oxide - Woodward and Woodward (1971) noted anemia in dogs injected subcutaneously with ethylene oxide saline solutions of 6 to 36 mg/kg daily for 30 days. The severity of this effect was dose related. Pathology showed hyperplastic bone marrow and ectopic hematopoiesis. Balazs (1976) was unable to repeat these effects in beagle dogs with ethylene oxide-glucose solutions injected intravenously over the same concentration range in a 21-day study. Apparently, differences in metabolism caused by the two routes of administration may be important.

Inhalation studies using several animal species exposed repeatedly to ethylene oxide vapor were conducted by Hollingsworth and coworkers (1956). All animals (rats, guinea pigs, mice, rabbits, and monkeys) died when exposed to ethylene oxide for eight periods of seven hours each at 841 ppm. Pathologic examination showed the same changes in the lungs, liver, and kidneys as observed after acute lethal exposures to ethylene oxide. In a second experiment rats and mice were exposed to 357 ppm ethylene oxide. Death in most animals was observed after 33 to 38 exposures (7 hrs) and was attributed to secondary respiratory infections. Impairment of sensory and motor function of the nervous system at the sacral and lumbar region level was observed in the latter period of this study, resulting in paralysis and atrophy of the hind leg muscles. Surviving animals showed reversal of the paralytic symptoms in the next 100 to 132 days. Guinea pigs survived 123 exposures to this concentration of ethylene oxide (357 ppm). Growth depression was seen, as well as degeneration of the testicular tubules in males and slight fatty degeneration of the adrenal cortex in females. No nervous system effects were seen in the guinea pigs. Four monkeys exposed to this level of ethylene oxide for 38 to 94 times did show the paralysis and muscular atrophy of the hind limbs previously described. Rats subjected to repeated (127 to 133) seven-hour exposures of 204 ppm ethylene oxide showed weight loss, some deaths, and effects on the lungs, kidneys, and testes. These included congestion of the lungs, slight cloudy swelling of some of the convoluted tubules, and slight degeneration of a few testicular tubules.

In an inhalation study with ethylene oxide, Jacobsen and coworkers (1956) exposed several species of animals for six hours per day, five days a week. Dogs given six weeks of exposure to 292 ppm ethylene oxide showed significant hematological changes. These included a decrease in red blood cells, hemoglobin, and hematocrit. Two dogs showed symptoms of anemia following six months' exposure to 100 ppm ethylene oxide.

An oral feeding study using 10% ethylene oxide in olive oil was performed on rats (Hollingsworth et al., 1956). Rats fed 100 mg/kg ethylene oxide in 15 doses over 21 days showed marked weight loss, gastric irritation, and slight liver damage. Feeding of 30 mg/kg in 22 doses produced no observable adverse effects.

Rats injected subcutaneously with ethylene oxide at a dose level of 54 mg/kg daily for 30 days showed weight loss and injection site hemorrhage and inflammation. Ethylene oxide administered at 18 mg/kg for the same schedule produced no observed toxicity (Hollingsworth et al., 1956).

Propylene Oxide - Rowe and coworkers (1956) performed experiments on repeated inhalation exposure to propylene oxide vapor. Guinea pigs, rabbits, and one monkey survived 79 to 154 seven-hour exposures to 457 ppm propylene oxide. Rats showed increased mortality due to the development of pneumonia. Pathology done on these animals revealed slight alveolar hemorrhage and edema, congestion of the lungs, and slight fatty degeneration of the liver (guinea pigs). At the level of 195 ppm, propylene oxide administered for 128 to 154 seven-hour exposures did not induce observable toxic effects.

Feeding studies with 10% propylene oxide in olive oil were conducted by this same group. Following 18 doses of 300 mg/kg propylene oxide, rats showed slight weight loss, gastric irritation, and slight liver damage. Comparable studies at 200 mg/kg did not produce observable toxicity.

Subacute vapor inhalation studies with propylene oxide were conducted by Midwest Research Institute (1976) for Tracor Jitco Inc. Mice were exposed for six hours per day for 63 days to propylene oxide vapor. At the highest level tested, 500 ppm, there were no deaths. A significant ($p<0.01$) weight loss was observed in these animals, but no histopathologic changes could be seen upon tissue examination. Rats treated under the same schedule also showed total weight loss at the highest level of propylene oxide vapor tested (500 ppm).

Butylene Oxide - Hine and Rowe (1973) reported that rats, guinea pigs, and rabbits can tolerate repeated seven-hour exposures to butylene oxide at a concentration of 400 ppm. These vapor studies indicate that butylene oxide is less toxic than ethylene oxide after inhalation, and possibly less toxic than propylene oxide.

Diepoxybutane - Skin painting of mice with ∿40 mg/kg d,l-diepoxybutane or meso-diepoxybutane three times per week produced noticeable toxicity. Median survival times were 78 and 154 days, respectively (Van Duuren et al., 1963, see Section III.C.1.g).

Hendry and coworkers (1951) injected rats intraperitoneally twice weekly for 6 to 7 weeks with 20 mg/kg d,l-diepoxybutane, and then twice weekly for another six weeks with 10 mg/kg. All test animals were dead within 18 months after the start of treatment. Loss of spermatogenesis was observed in the testes of one mouse.

Diepoxybutane (mixed isomers) was painted on mouse skin daily for nine applications in two weeks (Weil et al., 1963). Concentrations of 5% and 10% diepoxybutane in acetone significantly suppressed the number of sebaceous glands. Intense hyperkeratosis and hyperplasia have been noted after skin painting with diepoxybutane as well as the development of sarcomas (see Section III.C.1.g).

Hine and Rowe (1973) reported that rats injected i.m. with 25 mg/kg of diepoxybutane showed leukopenia and lymphopenia following six treatments.

d) Chronic Toxicity

Diepoxybutane (mixed isomers) was administered intragastrically in tricaprylin to rats once weekly for a year (Van Duuren et al., 1966). At the level used, ∿10 mg/kg, no decrease in median survival time was observed in the rats tested. Since this study was undertaken to study the carcinogenic activity of diepoxybutane, the determination of complete toxic effects was not made.

e) Mutagenicity

Ethylene Oxide - The mutagenic effects of ethylene oxide in the Ames *Salmonella* assay are summarized in Table 26. Rannug and coworkers (1976) investigated the mutagenicity of ethylene oxide dissolved in cold ethanol using the Ames assay (*Salmonella typhimurium*). Ethylene oxide (9.55 m*M*) produced reverse mutations in tester strain TA 1535, indicating effects on base-pair substitution. Higher concentrations produced a dose-dependent increase in the number of mutations. No S-9 microsomal activation mix was required to produce this effect, indicating that ethylene oxide is a direct-acting mutagen.

Taylor (1979) tested the mutagenic activity of ethylene oxide gas in several Ames assay tester strains. At concentrations between 10 ppm and 100 ppm, ethylene oxide increased the number of mutants in tester strains TA 1535 and TA 100 in a dose-dependent relationship, without S-9 activation. Addition of S-9 mix increased the number of mutations observed. Ethylene oxide was thus effective in producing mutations both with and without metabolic activation. Experiments (unpublished) by Kauhanen (1977) at the Stanford Research Institute also indicate that ethylene oxide gives positive results in the Ames mutagenesis assay in a dose-dependent manner in tester strains TA 1535 and TA 100. Ethylene oxide concentrations from 0.01% to 0.1% produced mutations without S-9 mix. Preliminary results reported by Embree and Hine (1975) indicated that ethylene oxide produced base-pair substitution type mutations in the Ames system in tester strain TA 1535 without activation.

Ethylene oxide has been shown to produce mutations in a wide variety of other test systems. Sulovska and coworkers (1969) have shown a ten-fold mutation increase in pollen grains of barley plants exposed for 24 hours to 100 ppm ethylene oxide. Moutschen and coworkers (1968) showed a

Table 26 Ames Mutagenicity Assay for Ethylene Oxide

Number of Revertants Per Plate

Compound	Application Route	Tester Strain	Type of Activation	S-9 Source, Concentration	Minus S-9 Activation	Pre-incubation	Controls +S-9	Controls -S-9	Reference
Ethylene oxide	vapor	TA 1535	Aroclor	Rat liver 20 μℓ		--			Taylor (1979)
1 ppm				16	21		7	12	
5 ppm				35	28				
10 ppm				93	80				
50 ppm				520	371				
100 ppm				72000	592				
	vapor	TA 100	Aroclor	Rat liver 20 μℓ		--			Taylor (1979)
1 ppm				183	190		187	215	
5 ppm				249	251				
10 ppm				531	442				
50 ppm				968	396				
100 ppm				1928	1640				
	growth medium	TA 1535	--	--		yes	--	6.8	Rannug et al. (1976)
.96 mM					7.4				
4.77 mM					13.4				
9.55 mM					17.4				
47.70 mM					42.8				
95.50 mM					106.2				

dose-related increase in anaphase and metaphase chromosome aberrations in barley seeds exposed for 10 hours to 2.5 mM to 25 mM ethylene oxide. Back mutations (∿1000) were induced at the adenine loucus of *Neurospora crassa* by a 15 minute exposure of the mold to 0.025 M ethylene oxide (Kolmark and Westergaard, 1953). Blixt and coworkers (1958) produced a high rate of mutation (26.7%) in field peas exposed for five hours to ∿30 mM ethylene oxide.

Studies with *Drosophila melanogaster* (Fahmy and Fahmy, 1970) have shown that ethylene oxide (114 mM) microinjected into adults produces point mutations, chromosome deletions, and chromosome breaks. Ethylene oxide (0.8%) injected into *Drosophila* was also shown to increase the number of lethal mutations observed (Bird, 1952).

Lambda bacteriophage has been induced in *Escherichia coli* after a 30 minute exposure of *E. coli* containing this prophage to 15 mM ethylene oxide (Hussain and Ehrenberg, 1975). Loveless and Wheatley (1966) were unable to show mutations induced in the r II region of T_4 bacteriophage after treatment with 0.1 M ethylene oxide for 10 minutes.

The mutagenicity of ethylene oxide has been evaluated by Embree and Hine (1975) in several mammalian assay systems. Rats exposed to ethylene oxide inhalation for four hours at 1000 ppm showed mutagenic effects in the dominant lethal assay. Ethylene oxide produced an increase in the ratio of dead implants to total implants but did not increase preimplantation losses. Rats exposed to 250 ppm ethylene oxide by inhalation seven hours per day for three days showed mutagenic effects in bone marrow samples. Twenty-four hours after exposure these bone marrow samples showed increased chromatid and isochromatid gaps, increased breaks, rearrangements and exchanges, and increased chromatid rings. Total aberrations were increased from 6% to 84% in metaphases examined. Examination of erythrocytes indicated that ethylene oxide induced an increase in red blood cells with micronuclei following a single four-hour exposure to concentrations of 50 to 1000 ppm. Experiments conducted by Appelgren and coworkers (1978) using this micronucleus test indicated ethylene oxide-induced mutations in both mice and rats. Ethylene oxide (aqueous) administered intravenously twice (30 hrs and 6 hrs before sacrifice) at a dose of 100 mg/kg increased ($p<0.05$) the proportion of polychromatic erythrocytes showing micronuclei in the test animals. This effect was shown to be dose dependent in mice. Severe bone marrow depression in rats prevented testing of ethylene oxide over an extended concentration range.

Strekalova (1971) reported that oral administration of 9 mg/kg of aqueous ethylene oxide produced increased chromosomal fragments and bridges in rat femur bone marrow at 24 and 48 hours following exposure.

In chronic inhalation studies, Strekalova and coworkers (1975) continuously exposed male rats to 2 ppm and 62 ppm ethylene oxide for 66 days. Both levels produced an increase in fetal deaths in untreated pregnant rats.

Propylene Oxide - Loveless and Wheatley (1966), citing the early studies of Rappaport, reported that propylene oxide, like ethylene oxide, will induce sex-linked lethal mutations in *Drosophilia*. Brief immersion of flies into a 10% propylene oxide solution increased the mutation rate tenfold. Back mutations at the adenine locus of *Neurospora crassa* were produced after treatment with 0.5 *M* propylene oxide (aqueous) for 15 minutes (Kolmark and Giles, 1955).

Wade and coworkers (1978) investigated the mutagenicity of propylene oxide in the Ames assay (see Table 27). The compound, dissolved in dimethyl sulfoxide, was incorporated into the top agar layer. At concentrations

Table 27. Ames Mutagenicity Assay for Epoxides and Reaction Products

Number of Revertants Per Plate, Ames Mutagenicity Assay

Compound	Application Route	Tester Strain	Type of Activation	S-9 Source, Concentration	Minus S-9 Activation	Pre-incubation	Controls +S-9	Controls -S-9	Reference
Chloropropanol (mixed isomer)	Agar Overlay	TA 1530	--	--		--	--	22	Rosenkranz et al. (1975)
1.1 mg					32				
2.2 mg					37				
5.5 mg					89				
11.0 mg					182				
16.5 mg					224				
22 mg					305				
Butylene oxide	Agar Overlay	TA 100	--	--		--	--	72	Speck and Rosenkranz (1976
14 mg					430				
16 mg	Agar Overlay	TA 1530	--	--	506		--	10	Chen et al. (1975)
4.2 mg	Agar Overlay	TA 1535	--	--	333		--	20	McCann et al. (1975)
.8 mg	Agar Overlay	TA 1535	--	Rat liver, 400 µg/plate					Rosenkranz and Poirer (1979)
				164	428		12	9	
Diepoxybutane	Agar Overlay	TA 1535	--	--		--			
25 µg					~120			~40	Simmon (1979a)
50 µg	Agar Overlay	TA 1535	--	--	91			20	McCann et al. (1975)
	Paper Disc	TA 1535	--	Rat liver, 400 µg/plate		--	18	21	Rosenkranz and Poirer (1979)
22 µg				66	140				
66 µg				134	488				
110 µg				218	914				
Propylene oxide	Agar Overlay	TA 100					--	180	Wade et al. (1978)
1.5 mg			--	--	346	--			
1 mg	Agar Overlay	TA 1535	--	--	42	--	--	20	Wade et al. (1978)

of 1 to 1.5 mg propylene oxide per plate, both tester strains TA 100 and TA 1535 showed increased revertants over controls without activation. No dose response data were presented, but values reported were taken from the midpoint of the linear portion of a dose-response curve generated with the compound. Mutagenicity in TA 100 was 166 revertants/1500 μg compound. The reaction product of propylene oxide, chloropropanol, has been shown to increase mutations in tester strain TA 1530 by Rosenkranz and coworkers (1975) (see Table 27).

Butylene Oxide - The mutagenic effects of butylene oxide in the Ames assay are summarized in Table 27.

Investigation of the mutagenicity of butylene oxide in the Ames assay was performed by Speck and Rosenkranz (1976). Butylene oxide (14 μg) incorporated into the agar overlay without S-9 activation produced approximately 350 more revertants than the control when tester strain TA 100 was used. Other work from this laboratory inciated that comparable levels of mutations are produced by butylene oxide applied to tester strains TA 1530 (Chen *et al*., 1975) and the nitrofurazone-resistant tester strain TA 100-FRI (Rosenkranz and Speck, 1975). In a recent report Rosenkranz and Poirer (1979) showed a dose-dependent increase in mutations produced by butylene oxide applied to the agar overlay with tester strain TA 1535. Addition of S-9 activation mix prepared from the livers of uninduced rats produced a decrease in mutants seen with all concentrations of butylene oxide. Metabolic conversion by microsomal enzymes therefore seems to inactivate the butylene oxide in this test system.

Simmon (1979a) was unable to show mutagenic activity after application of butylene oxide to any of the *Salmonella* test strains used

(TA 1535, 1538, 1537, 1536, 98, and 100) either with or without activation. The compound was tested at concentrations up to 500 μg/plate. However, in another study Simmon (1979b) did show increased mutation in Saccharomyces cerevisiae D3 after treatment with butylene oxide. Applications of 0.6% butylene oxide to Saccharomyces produced 1500 recombinants at the adenine 2 locus; inclusion of S-9 activation mix prepared from livers of Aroclor-pretreated rats reduced the number of mutations observed.

Butylene oxide has been tested for its ability to modify DNA in E. coli DNA polymerase deficient strains (Rosenkranz and Poirer, 1979). Comparison of the zones of inhibition produced by application of butylene oxide (50 μg/ml) to E. coli strains with or without normal production of this DNA repair enzyme indicates that the compound does damage DNA. This assay correlates well with the mutagenic activity determined by the Ames Salmonella assay.

Diepoxybutane - Diepoxybutane was found to produce lethal mutations in barley seeds (Ehrenberg and Gustaffson, 1957) after application of a 0.003% aqueous solution for two hours. Comparison of effects on germination relative to those produced by ethylene oxide indicates that diepoxybutane is approximately 200 times more effective in mutation induction in this assay. Bianchi and Contin (1962) studied the mutagenic effects of diepoxybutane on pollen from maize following treatment with 0.15 to 0.25 percent solutions of the compound. Endosperm mutation frequencies indicated that the racemic diepoxybutane was the most effective mutagen, followed in relative order by the l-isomer, the d-isomer, and the meso-isomer.

Administration of diepoxybutane to Drosophilia by feeding or injection into the hemocoel produced varied mutations (Bird and Fahmy, 1953). These included lethal mutations, semi-lethal mutations, visible mutations, translocations, and "minute" type chromosome breaks.

Hendry and coworkers (1951) reported that diepoxybutane-treated (0.25 percent aqueous solution) spores of Penicillium mold showed an increase in the percentage of mutant colonies. Diepoxybutane-induced mutations at the adenine locus of *Neurospora* were seen after treatment of the conidia with 0.2 *M* compound for 15 minutes (Kolmark and Westergaard, 1953).

Heinemann and Howard (1964) activated lambda bacteriophage in *Escherichia coli* following one hour treatment of cultures with diepoxybutane at a concentration of 7.5 µg/ml. Mutations in *Saccharomyces cerevisiae* have been reported following five hours of treatment with 0.005 M diepoxybutane solution (Zimmermann, 1971).

Diepoxybutane has been shown to increase the number of histidine revertants in the Ames assay (McCann *et al*., 1975) (see Table 27). Fifty micrograms of compound per plate produced mutations in tester strain TA 1535 without S-9 activation. Rosenkranz and Poirer (1979) found a dose-dependent increase in mutations produced in tester strains TA 1535 and 1538; addition of S-9 activation mix lowered the number of mutants seen. Simmon (1979) reported that addition of 25 µg of diepoxybutane per plate increased histidine revertants in tester strain TA 1535; this level of compound produced a very weak level of activity in tester strain TA 100.

Simmon and coworkers (1979) investigated the activity of diepoxybutane in the host mediated assay. Diepoxybutane injected intramuscularly into mice at a concentration of 444 mg/kg produced an increase in the mutation frequency of *Salmonella* strain TA 1530 that was injected intraperitoneally into the same animals. At a lower treatment level (56 mg/kg) no increase in mutations was seen in tester strain TA 1535. *Saccharomyces cerevisiae* D3 injected into the peritonum of treated mice did show an increase in mutation frequency at this level of exposure.

Rosenkranz and Poirer (1979) reported increased inhibition of DNA polymerase deficient E. coli strains after application of diepoxybutane, indicating modification of the DNA of these strains. Simmon (1979b) observed increased numbers of recombinants in S. cerevesiae D3, with or without S-9 activation, after treatment with a 0.04% solution of diepoxybutane.

Mammalian systems also show increased genetic damage following exposure to diepoxybutane. Moutschen (1961) evaluated the effects of diepoxybutane on murine sperm chromosomes. Mice injected intraperitoneally with 5 mg/kg diepoxybutane showed chromosome effects in 24 hours. This included increased chromosome breaks and anaphase bridges. At 20 days following administration of diepoxybutane these changes were no longer significant relative to controls, indicating an efficient repair of this type of chromosome lesion.

The dominant lethal assay in the mouse has been used to evaluate the mutagenicity of diepoxybutane (Epstein et al., 1972). Injection of male mice with 17 mg/kg (intraperitoneal) diepoxybutane produced an increase in the percentage of impregnated females with early deaths; however, early fetal deaths and preimplantation losses were within the variance range of controls.

f) Teratogenicity and Reproductive Effects

Ethylene Oxide - In a study of teratogenic effects induced by inhalation of ethylene oxide, Snellings and coworkers (1979) exposed rats from day 6 to day 15 of gestation to 10 to 100 ppm ethylene oxide (6 hrs/day). Evaluation of day 20 fetuses showed no developmental effects other than a reduced body weight in the 100 ppm group. The reproductive effects were studied following exposure of male and female weanling rats to 10 to 100 ppm ethylene oxide six hours per day, five days per week, for 12 weeks. Animals were mated and ethylene oxide exposure was continued through day 19 of gestation. Female rats exposed to 100 ppm ethylene oxide had a longer gestation period, reduced fertility index, and significantly fewer pups per litter. No differences were found for gestation survival or postpartum survival. The effects seen are probably the result of the nonspecific toxicity produced by this level of ethylene oxide inhalation.

Kimmel and Laborde (1979) studied the effects of ethylene oxide when injected intravenously into the tail veins of female mice. Doses of 75 mg/kg and 150 mg/kg ethylene oxide in saline were injected daily for three days at four periods during gestation: days 4-6, 6-8, 8-10, and 10-12. Mice receiving 150 mg/kg showed toxic symptoms (unspecified) during treatment but recovered and showed no ultimate change in maternal weight gain during pregnancy. Litters were examined at day 17 of gestation. Animals treated during the first and last gestation periods with ethylene oxide showed an increase in the percentage of resorptions. Significant increases in malformations were seen in animals treated on days 6-10 of gestation at the high (150 mg/kg) ethylene oxide level. Malformations noted included fused vertebral arches, fused and branched ribs, scrambled sternabrae, and some exencephaly. Embryotoxicity and teratogenicity are thus indicated by this route of exposure to ethylene oxide.

Chloroethanol, a potential reaction product of ethylene oxide, has produced teratogenic effects when injected into the air sack of chick embryos (Versett, 1974) at levels of 5 to 50 mg per egg.

Hollingsworth and coworkers (1956) observed effects of ethylene oxide on the testes of guinea pigs. Animals inhaling 357 ppm ethylene oxide during 123 seven-hour exposures showed tubular degeneration and fibrosis of the testes. Rats exposed to 204 ppm ethylene oxide for 122 to 157 seven-hour periods showed decreased size of testes and some tubular degeneration. Whole body autoradiographs of mice injected with radioactive ethylene oxide indicate that this compound accumulates in the epididymis and testes (Appelgren et al., 1977).

Diepoxybutane - Epstein and coworkers (1972) investigated the effects of diepoxybutane in the dominant lethal assay. Male mice were injected intraperitoneally with 17 mg/kg of diepoxybutane and then mated for several weeks with virgin females. Pregnant females showed an increased rate of early fetal deaths in this study. Effects on implantation were not seen. Prolonged exposure of rats to high levels of diepoxybutane (10 to 20 mg/kg, 26 doses) produced loss of spermatogenesis in one test animal (Hendry et al., 1951).

g) Carcinogenicity

Ethylene Oxide - The carcinogenic effects of ethylene oxide are summarized in Table 28.

In a study of the carcinogenicity of ethylene oxide dissolved in arachis oil, Walpole (1958) injected rats subcutaneously with a maximum total dose of 1 gm/kg of ethylene oxide over 94 days (dosing schedule not specified) and found no tumors induced. Rats were observed for their lifetime following treatment. Since the amount administered and the frequency of injection was not specified, it is difficult to evaluate these negative results. Tumors were induced by the same technique with propylene oxide, but duration of treatment was much longer.

Lifetime skin painting studies with 10% ethylene oxide in acetone (3 times weekly) were performed on female mice by Van Duuren et al.

Table 28. Carcinogenesis Bioassay of Ethylene Oxide

Route	Species, Sex	Dosage	Duration of Treatment	Duration of Observation	Premature Deaths	Controls	Tumors	Reference
S.c.	Rat, M,F	1000 mg total (oil)	94	Lifetime	No	Pos. ? Neg. ?	Sarcoma - 0	Walpole (1958)
Dermal	Mouse, F	10 mg/animal	3 time/wk life	Lifetime (493 days)	No	Pos. yes Neg. yes	Papilloma-0 Carcinoma-0	Van Duuren _et_ _al_. (1965)

(1965). Application of 0.1 ml of ethylene oxide solution to the clipped dorsal skin produced no tumors. Median survival time for the mice was 493 days. The investigators indicated that rapid evaporation of the compound from the skin could have been responsible for the negative results observed.

Reyniers and coworkers (1964) conducted a retrospective study on female germ-free mice that developed tumors after being exposed to ethylene oxide-treated ground-corncob bedding for 150 days. Ovarian, lymphoid, and pulmonary tumors developed in these animals after being moved to untreated bedding. Colony mates maintained on nontreated bedding did not develop tumors. All the males exposed to ethylene oxide-treated bedding died, with necropsy showing massive hemorrhage. The causative agent was not identified since chemical analysis of the bedding was not done. High toxicity is indicated by these findings in the male mice. Because germ-free mice are T-lymphocyte deficient, they may be more susceptible to tumor development than normal animals.

A long-term carcinogenicity bioassay to study the effects of inhalation exposure to ethylene oxide is currently underway at Carnegie-Mellon Institute. Carcinogenicity studies on the effects of skin painting with ethylene oxide are scheduled to begin for the National Cancer Institute.

Propylene Oxide - Carcinogenic effects of propylene oxide are summarized in Table 29.

Injection of propylene oxide subcutaneously into rats was shown to produce local (injection site) sarcomas (Walpole, 1958). Propylene oxide dissolved in arachis oil or water was injected over 325 days for a total maximum dosage of 1.5 gm/kg (schedule not specified). Eight of the animals administered propylene oxide in oil developed tumors in 507 to 739 days. Three of the animals

Table 29. Carcinogenesis Bioassay of Propylene Oxide

Route	Species, Sex	Dosage	Duration of Treatment	Duration of Observation	Premature Deaths	Controls	Tumors	Reference
S.c.	Rat, M,F	1500 mg total (H_2O)	325 days	739 days	No	Pos. ? Neg. ?	Sarcoma-3	Walpole (1958)
S.c.	Rat, M,F	1500 mg total (oil)	325 days	737 days	No	Pos. ? Neg. ?	Sarcoma-8	Walpole (1958)

receiving the aqueous solution of the compound developed sarcomas, one in 158 days and the other two after 737 days. These tumors (except one at 158 days) were quite late in developing. Since the schedule of administration is not known and control data were not reported, evaluation of these data is not possible.

Butylene Oxide - The carcinogenicity of butylene oxide was studied by Van Duuren and coworkers (1967) following extended skin painting of mice (see Table 30). Approximately 100 mg of butylene oxide (10% in acetone) was applied three times weekly to clipped mouse skin for 540 days. This schedule of application did not produce toxicity in the test animals, and skin tumors were not seen during the time period indicated. The late development of injection site tumors observed by Walpole (1958) after subcutaneous injection of propylene oxide suggests that a similar extended latency period for tumors may follow butylene oxide treatment. These may be missed if the experimental protocol is not optimized for long term observation of test animals.

Diepoxybutane - Carcinogenic effects of diepoxybutane are summarized in Table 31.

McCammon and coworkers (1957) reported that skin painting of mice with d,l-diepoxybutane produced tumors. The compound was applied three times weekly by intrascapular painting. Total dose and duration of treatment were not reported, nor was the incidence of tumors. Subcutaneous injection of diepoxybutane into rats was also reported to increase tumor incidence.

Lifetime mouse skin painting studies with d,l-diepoxybutane were performed by Weil and coworkers (1963). Mice received three applications per week of 10% diepoxybutane in acetone. Two papillomas and one carcinoma were produced by this method, with a median latent period of 18.5 months. This regime

Table 30. Carcinogenesis Bioassay of Butylene Oxide

Route	Species, Sex	Dosage	Duration of Treatment	Duration of Observation	Premature Deaths	Controls	Tumors	Reference
Dermal	Mouse, F	10 mg/animal	3 times/wk life	Lifetime (540 days)	No	Pos. yes Neg. yes	Papilloma-0 Carcinoma-0	Van Duuren *et al.* (1967)

Table 31. Carcinogenesis Bioassay of Diepoxybutane

Route	Species, Sex	Dosage	Duration of Treatment	Duration of Observation	Premature Deaths	Controls	Tumors	Reference
Dermal	mouse, M,F	10% in acetone	3 times/wk, 20 months	Lifetime	Yes 22/25	Neg. ? Pos. yes	Papilloma-2 Carcinoma-1	Weil et al. (1963)
I.p.	rat, M,F	20 mg/kg, 10 mg/kg	13 doses high 12 doses low	18 months	Yes 14/14	Neg. ? Pos. ?	Sarcoma-1	Hendry et al. (1951)
I.p.	mouse, M,F	16 mg/kg (L form)	3 times/wk 4 weeks	39 weeks	Yes 3/30	Neg. 32% tumors Pos. yes	lung tumors 78%	Shimkin et al. (1966)
Dermal	mouse, M	10 mg/animal (meso form)	3 times/wk life	Lifetime (154 days)	Yes 30/30	Neg. yes Pos. yes	Papilloma-6 Carcinoma-4	Van Duuren et al. (1963)
Dermal	mouse, M	10 mg/animal	3 times/wk life	Lifetime (78 days)	Yes 30/30	Neg. yes Pos. yes	Papilloma-2 Carcinoma-1	Van Duuren et al. (1963)
Dermal	mouse, F	10 mg/animal	3 times/wk life	Lifetime (165 days)	Yes 30/30	Neg. yes Pos. yes	Papilloma-1 Carcinoma-0	Van Duuren et al. (1965)
Dermal	mouse, F	3 mg/animal	3 times/wk life	Lifetime (475 days)	No	Neg. yes Pos. yes	Papilloma-10 Carcinoma-6	Van Duuren et al. (1965)
Dermal	mouse, F	10 mg/animal (meso form)	3 times/wk life	Lifetime (357 days)	No	Neg. yes Pos. yes	Papilloma-5 Carcinoma-4	Van Duuren et al. (1965)
Dermal	mouse, F	3 mg/animal (meso form)	3 times/wk life	Lifetime (491 days)	No	Neg. yes Pos. yes	Papilloma-1 Carcinoma-0	Van Duuren et al. (1965)
S.c.	mouse, F	1.1 mg/ animal	1 time/wk life	Lifetime (328 days)	No	Neg. yes Pos. yes	Papilloma-0 Sarcoma-5	Van Duuren et al. (1966)
S.c.	mouse, F	0.1 mg/ animal	1 time/wk life	Lifetime (456 days)	No	Neg. yes Pos. yes	Papilloma-0 Sarcoma-5	Van Duuren et al. (1966)
S.c.	rat, F	1 mg/animal	1 time/wk life	Lifetime (470 days)	No	Neg. yes Pos. yes	Carcinoma-1 Sarcoma-9	Van Duuren et al. (1966)
Dermal	mouse, F	1 mg/animal	single + phorbol ester 3 times/wk, life	Lifetime	No	Neg. yes Pos. yes	Papilloma-7 Carcinoma-2	Van Duuren (1969)
Dermal	mouse, F	1 mg/animal (meso form)	single + phorbol ester 3 times/wk, life	Lifetime	No	Neg. yes Pos. yes	Papilloma-4 Carcinoma-0	Van Duuren (1969)

was quite toxic since only three mice were still alive at 18 months. Negative control data for these animals were not reported.

Van Duuren and coworkers (1963) tested both the mixed d,l-isomer of diepoxybutane and the meso isomer of the compound for carcinogenicity by skin painting. Acetone solutions of both the mixed isomer and the meso form were applied (10 mg per animal) to the clipped dorsal skin of male mice, three times weekly for life. Following application of d,l-diepoxybutane, two mice developed skin tumors; one of these was a squamous cell carcinoma. Squamous cell carcinomas were also seen in 4/6 mice which developed tumors after application of meso-diepoxybutane. The dose schedule used in these studies produced toxicity, since the median survival times of treated animals were markedly shorter than those seen for controls (78 days lifespan for the mixed isomer and 154 days for the meso isomer group). Late developing tumors would be missed under these conditions.

These studies were therefore repeated using lower levels of the d,l and meso isomers of diepoxybutane applied by skin painting to female mice by the same schedule (Van Duuren et al., 1965). At a dose of 10 mg per animal, one of thirty mice treated with d,l-diepoxybutane developed a skin papilloma. Median survival time (165 days) was shortened at this level of treatment, again indicating a significant toxic effect that confuses interpretation of the dose-response relationship. Mice given d,l-diepoxybutane at the level of 3 mg per animal developed tumors (16/30); of these 16, six showed squamous cell carcinomas. Median survival time was 475 days for this group. Meso-diepoxybutane tested at the same dosages produced five incidences of skin papilloma and four of squamous cell carcinoma at the 10 mg per animal level. The low-dose application of meso-diepoxybutane produced one incidence of a skin papilloma. Median survival times for the groups treated with the meso compound were comparable to control values. Skin irritation was severe after administration of the mixed isomer diepoxybutane and moderate following application of the meso compound.

Intraperitoneal injection of the mixed isomer diepoxybutane into rats reportedly produced one case of sarcoma development (Hendry et al., 1951). Ten male and four female rats were injected with 20 mg/kg of diepoxybutane in arachis oil twice weekly for 13 doses, and then with 10 mg/kg twice weekly for another 12 doses. All animals were dead at 18 months from the start of treatment. Necropsy in one animal that died at 13 months showed large masses of a mixed cell sarcoma.

Bird and Fahmy (1953) injected rats subcutaneously with mixed isomer diepoxybutane in arachis oil at the level of 2 mg per animal, once weekly for 16 weeks. Positive results in the production of sarcomas were reported, but no experimental details were published.

Diepoxybutane was tested for carcinogenicity in mice and rats by subcutaneous injection (Van Duuren et al., 1966). Female mice were injected with d,l-diepoxybutane in tricaprylin at 0.1 or 1.1 mg per animal once weekly for over one year. Tumor latency was eight to 12 months. At the lower dose level, five of 30 animals developed fibrosarcomas and two of 30 animals developed adenocarcinomas. Five of 30 animals developed fibrosarcomas at the higher dose level. Survival time was comparable to controls. In the study with rats, animals were injected subcutaneously with 1 mg, once weekly for over one year. Out of a test group of 50 animals, ten animals developed tumors, including nine with fibrosarcomas and one with an adenocarcinoma. Median cumulative dose of d,l-diepoxybutane in this study was 67 mg of compound. Gastric feeding studies were performed with each rat receiving 5 mg of d,l-diepoxybutane in tricaprylin once weekly for life. Median survival time of treated animals was 342 days compared to 525 days for controls. No tumors were detected by this feeding study.

Shimkin and coworkers (1966) studied the effects of l-diepoxybutane on the development of pulmonary tumors in strain A mice. The l-isomer of diepoxybutane was dissolved in either water or tricaprylin and injected three times weekly (i.p.) into mice for 12 weeks. Total doses in water were 1.7, 6.7, 27, 108, and 192 mg/kg, with resulting tumor incidences of 21, 40, 55, 64, and 78%, respectively, at 39 weeks after treatment. Total doses in tricaprylin were 3, 12, 48, and 192 mg/kg, which produced tumor incidences of 40, 43, 46, and 50%. Controls showed a spontaneous rate of lung tumor development of 35%. Significant tumor increases were seen at the three highest dose levels in water. This test evaluates the acceleration of lung tumor development rather than the actual induction of tumors, and has been designed as a short term in vivo carcinogenicity screening assay.

The mixed d,l-isomer of diepoxybutane and the meso-isomer have both been tested for tumor initiating activity by Van Duuren (1969). Following an initial application of 1 mg of compound in 0.1 ml of acetone to mouse skin, phorbol ester was applied three times weekly for life, beginning two weeks after initiation. Twenty mice that received d,l-diepoxybutane showed seven cases of papilloma and two cases of carcinoma. Following administration of the meso compound four mice developed papillomas. The incidence of tumors after initiation with either d,l or meso-diepoxybutane was increased relative to controls, which showed less than a 10% tumor development frequency.

h) Neurotoxicity

Subacute inhalation studies on the toxicity of 357 ppm ethylene oxide vapor (Hollingsworth et al., 1956) revealed neurotoxic effects after several weeks of exposure. Rats, rabbits, and monkeys showed paralysis and atrophy of the muscles of the hind limbs. These effects were reversible after discontinuation of exposure for 100 to 132 days. Special studies on monkeys were carried out with repeated (38 to 94) exposures to this level of ethylene oxide. Knee jerk reflexes became very weak, pain perception in the hind quarters decreased, the cremasteric reflex was elicited, and the extensor reflex of the palms of the hind feet was abolished. Impairment of both sensory and motor functions at the lumbar and sacral level of the spinal cord was indicated. Exposure of monkeys to a lower level of ethylene oxide (2.4 ppm for 176 to 226 days) produced partial paralysis and some muscular atrophy of the hind legs with moderate suppression of the leg reflexes. The Babinski reflex was present after this lower level exposure to ethylene oxide.

Balazs (1976) reported that dogs given the ethylene oxide reaction product 2-chloroethanol orally developed an abnormal posture of the hind legs in a subacute test. Chloroethanol given to cats subcutaneously at 10 mg/kg on three consecutive days produced decreased performance in a conditioned reflex test.

2. Toxicity and Effects on Other Vertebrates

The effects of these epoxides on other vertebrates have not been characterized.

3. Toxicity and Effects on Invertebrates

Ethylene oxide has been utilized as a fumigant for foods and spices and shows major insecticidal activity (Lindgren and Vincent, 1966). Susceptible insects common to stored products include the flour beetle, rice weevil, and grain weevil (Lindgren *et al.*, 1954). Ethylene oxide will kill one-half the stored product insect population at a concentration range of 6 to 18 mg/liter, while propylene oxide is effective at 25 to 32 mg/liter (Ong, 1948).

Lindgren and Vincent (1966) reported a major reduction in available tissue glutathione content of Calliphora larvae exposed to ethylene oxide. Decrease in tissue glutathione via depletion of reduced-SH groups may be the mechanism of toxicity. The insect toxicity of ethylene oxide has been ranked by Lindgren as intermediate between that of ethylene dibromide and ethylene dichloride. A bibliography of ethylene oxide insecticidal properties citing 185 references has been published (Young and Busbey, 1935).

Bird (1952) reported on the toxicity of ethylene oxide and diepoxybutane to Drosophila. Ethylene oxide injected into adult males at the level of 0.8% solution (arachis oil) killed half the population, while injection of a 0.1% solution of diepoxybutane killed approximately one half of the flies tested. Based on this comparison these investigators estimate that diepoxybutane is at least tenfold more toxic than ethylene oxide.

D. Toxicity and Effects on Plants

The epoxides are agents capable of producing mutations in plants by interaction with chromosomal materials (see Section III.1.g). Ehrenberg and coworkers (1959) found that treatment of barley seeds with 0.1 to 0.3% ethylene oxide solution produces increased mutations; some of these mutations are lethal and others induce sterility in the subsequent plants. Comparison of the effects of diepoxybutane and ethylene oxide solutions on barley seeds by Ehrenberg and Gustaffson (1957) indicated that 0.15% aqueous ethylene oxide exposure for two hours kills half the resting seeds treated, while 0.001% diepoxybutane treatment produces the same effect. Ark (1947) has reported that treatment of club wheat seeds with propylene oxide gas at the concentration of 35,000 ppm under vacuum for six hours produces a 50% loss in germination. The level of propylene oxide gas producing germination loss is generally higher than the level needed to kill associated pathogenic bacteria or fungi.

E. Toxicity and Effects on Microorganisms

Ethylene oxide and propylene oxide have been used to kill a wide variety of bacteria and fungi in foods and spices. Sykes (1964) reported that exposures to gaseous ethylene oxide at concentrations of 1 to 10% will kill *Bacillus globigii*, *Staphylococcus aureus*, *E. coli*, *Chromobacterium prodigiosum*, and *Mycobacterium phlei* within a few hours. Roberts and coworkers (1943) found that 10% gaseous ethylene oxide will kill *Bacillus anthracoides* in eight hours. A 5% gaseous concentration of ethylene oxide produced 90% kill of airborne *B. globigii* spores in less than two hours.

Skeehan (1959) indicated that herpes simplex, vaccinia, and bovine respiratory viruses are susceptible to saturated ethylene oxide vapor treatment.

Treatment of agar slants containing yeasts and fungi with 8% gaseous ethylene oxide for three hours was lethal to these microorganisms (Whelton *et al.*, 1946).

Ark (1947) reported that exposure of several types of pathogenic bacteria and fungi to 10% to 18% gaseous propylene oxide for one hour resulted in their inactivation.

Both propylene oxide and ethylene oxide produce significant sporicidal activity against dry bacterial spores (Bruch and Koesterer, 1961). Exposure of *Bacillus subtilis* spores to 1% to 2% vapor concentrations of ethylene oxide and propylene oxide killed 95% or more of the spores within four hours. Ethylene oxide produced a greater reduction in spore survival than did propylene oxide over short time periods.

Himmelfarb and coworkers (1962) tested the bactericidal activity of propylene oxide vapor on 16 strains. All strains tested were killed by varying the time of exposure (4 to 356 minutes) to 0.1% gaseous propylene oxide at a given relative humidity. Spores showed a greater resistance than vegetative forms to this treatment.

Exposure of bacteriophage T_2 to 2 M ethylene oxide solutions for four minutes has been shown to produce a 50% reduction in infectivity (Loveless and Wheatley, 1966).

F. In Vitro and Biochemical Studies

Ethylene oxide and propylene oxide have been shown to react with RNA isolated from tobacco mosaic virus (Fraenkel-Conrat, 1961). The site of alkylation has been proposed as the N-7 guanine position. Alkylation was increased in the presence of magnesium ion which induced a hypochromic state in the RNA structure.

Treatment of protein with ethylene oxide and propylene oxide has also led to chemical modifications (Fraenkel-Conrat, 1944). Egg albumin treated with 4.8% ethylene oxide or propylene oxide showed decreased amounts of reactive carboxyl, amino, phenol, and sulfhydryl groups. The majority of the reaction products formed after treatment with the epoxides were stable to both acid and alkali treatment.

Dent and Schnell (1979) studied the interaction of ethylene, propylene, and butylene oxides with epoxide hydratase. All three compounds produced inhibition of enzyme activity in vitro. The order of inhibition indicated that ethylene oxide was the most effective compound, but that it had a low order of affinity for the enzyme and thus was a weak competitive inhibitor.

Investigation of hemolysis produced by ethylene oxide (Jones, 1979) indicated that 2 mg/ml aqueous concentrations of the compound (2000 ppm) will lyse human red cells *in vitro*. Cultured mouse fibroblast cells showed toxicity when exposed to tubing containing residual ethylene oxide at the level of 2 mg/gm of tubing.

G. Effects on Foods

Windmueller and coworkers (1956) noted that rats fed diets fumigated with ethylene oxide suffered nutritional deficiencies. Examination of the casein from this treated chow showed destruction of major amounts of the amino acids, histidine and methionine, after 24 hours of ethylene oxide fumigation (concentration not indicated).

Investigation of the effect of saturated ethylene oxide vapor on dog meal indicated a significant loss of thiamine content (Bakerman *et al.*, 1956). Further examination of mixtures of vitamins and cornstarch exposed to saturated ethylene oxide in a dessicator for 18 hours indicated that thiamine, niacin, pyridoxine, riboflavin, and folic acid were all destroyed by this treatment. Hawk and Mickelsen (1955) also reported that rat chow exposed 12 to 24 hours to saturated ethylene oxide vapor treatment suffers from major loss of thiamine content. Growth defects in rats fed this treated diet can be reversed by the addition of thiamine.

H. Effects of the Compounds on Environmental Quality

The selected epoxides are potential hazards to soil microbial communities. Propylene oxide and ethylene oxide have been examined as soil sterilants (Skipper and Westingmann, 1973). Addition of 1 to 2 ml of propylene oxide was sufficient to sterilize 25 g soil samples. They also reported that the epoxide increased soil pH by 0.5 to 1.1 units. Propylene oxide apparently sterilizes soils by alkylation of functional groups in proteins of the microorganisms. Also, propylene oxide residues remain in the soil and hinder subsequent plant growth.

No adverse environmental effects, other than the hazard to microbial systems and possibly to plants, are anticipated.

I. Effects on Inanimate Objects

No information was available on effects of the selected epoxides to inanimate objects. It is anticipated that the epoxides could react with functional groups, for example, with cellulosic hydroxyl groups. Such reactions, which are known in the laboratory, could alter properties of some inanimate objects. Since effects have neither been documented nor been suggested elsewhere, this possibility is only hypothetical.

IV. CURRENT REGULATIONS

A. Federal, State, and Local Standards

1. Food, Drug, and Pesticide Authorities

Ethylene oxide and propylene oxide are applied as fumigants or sanitizers to a variety of products and thus are subject to appropriate regulations. Ethylene oxide is currently on the RPAR list. Both epoxides are applied as fumigants to bulk foods (including grains, cereals, nuts, and spices). Ethylene oxide is a sterilant which is applied to cosmetics, drugs, medical devices, single service food service items, and other products. The application limitations and tolerances established for their residues are described below. Tolerances in drugs and medical devices for ethylene oxide and its metabolites (ethylene chlorohydrin and ethylene glycol) are as follows (Federal Register, 1978):

(Parts per million)

Drug product	Ethylene oxide	Ethylene chlorohydrin	Ethylene glycol
Ophthalmics (for topical use)	10	20	60
Injectables (including veterinary intramammary infusions)	10	10	20
Intrauterine device (containing a drug)	5	10	10
Surgical scrub sponges (containing a drug)	25	250	500
Hard gelatin capsule shells	35	10	35

(Parts per million)

Medical device	Ethylene oxide	Ethylene chlorohydrin	Ethylene glycol
Implant:			
Small (<10 grams)	250	250	5,000
Medium (10-100 grams)	100	100	2,000
Large (>100 grams)	25	25	500
Intrauterine device	5	10	10
Intraocular lenses	25	25	100
Devices contacting mucosa	250	250	5,000
Devices contacting blood (ex vivo)	25	25	250
Devices contacting skin	250	250	5,000
Surgical scrub sponges	25	250	500

Ethylene oxide use with commodities and food service materials are subject to the following regulations:

> 21CFR178.3520 limits ethylene oxide to less than 3 pct of reacted ethylene oxide in finished industrial starch.
>
> 21CFR193.200 describes allowed application of ethylene oxide as fumigant for natural spices and establishes its tolerance at 50 ppm.
>
> 40CFR180.152 describes allowed application of ethylene oxide as a fumigant for black walnut meats, copra, whole spices, etc. and establishes its tolerance at 50 ppm.

Propylene oxide is subject to the following regulations:

> 21CFR193.380 describes its application as a package fumigant with dried prunes and glace fruit, and as fumigant for bulk cocoa, gums, spices, nutmeats (except peanuts), and starch. It also establishes a propylene oxide tolerance of 300 ppm.
>
> 21CFR172.890 describes its application to food starch modified in combination with epichlorohydrin (propylene oxide not to exceed 10%) and alone (not to exceed 25%).

The use of butylene oxide as an adjuvant substance for slime control in paperboard is described in 21CFR176.300.

2. Other EPA Authority

The selected epoxides are not specifically regulated by other EPA authorities. RCRA (43FR58946) classed waste pesticides (Group 2-A) as a source of toxic substance release in case of fire or explosion. This applies to the small amounts of ethylene oxide and propylene oxide formulated as pesticides.

3. OSHA

OSHA has set the TLV's for ethylene oxide and propylene oxide at 50 ppm (90 mg/cu m) and 100 ppm (240 mg/cu m), respectively.

4. DOT, ICC, CG - Transport Regulations

Ethylene oxide and propylene oxide are both classed as flammable liquids. Both require labels ("Flammable Liquid") and placarding as "Flammable." Ethylene oxide must be transported according to the DOT regulations for flammable liquids and packing specifications are described in 49CFR173.124 (ethylene oxide). Propylene oxide may be transported as flammable liquids with the exemption of 49CFR173.118. Its packing regulations are described in 49CFR173.119.

B. Concensus and Similar Standards

1. TLV

The American Conference of Governmental Industrial Hygenists (ACGIH, 1977) has set TLVs for ethylene oxide and propylene oxide at 50 ppm and 100 ppm, respectively and recently has recommended values of 10 and 20 ppm, respectively (Kurginski, 1979). The earlier values are the same as OSHA standards.

In 1965 the Dow Chemical Company provided some estimates for ethylene oxide and propylene oxide limits (Kereluk, 1971).

Exposure	Ethylene Oxide	Propylene Oxide
Daily, up to 8 hrs.	50	100
Single, for several hrs.	150	400
Single, for 1 hr.	500	1000

2. TWA

No TWAs have been established for the selected epoxides.

C. Current Handling Practices

1. Special Handling In Use

Ethylene oxide requires special handling in use because it is a gas at ambient temperature. Batch reactions should be carried out in a special kettle. The kettle should be fitted with pressurized feed lines from the ethylene oxide storage and it should be capable of maintaining the gas pressure generated during the process. Cooling and heating lines are required to initiate and maintain reaction (Jefferson Chemical, undated a).

Technical information on propylene oxide does not specify any special equipment for its handling (Jefferson Chemical Company, undated b; Oxirane Corporation, undated). Since propylene oxide is a liquid at ambient temperature, pressurization of reactors and feed lines from storage are not as critical as required for ethylene oxide. Batch reactors should be equipped with heating and cooling lines as described for ethylene oxide reactors.

Work areas, where ethylene oxide or propylene oxide are used, should be ventilated. Workers should wear appropriate protective clothing and respirators.

2. Storage and Transport Practices

Epoxide transport must follow DOT regulations. Propylene oxide should be shipped in unlined I.C.C.-17C drums (55 gal), or I.C.C.-105A and I.C.C.-111A 100-W-3 tank cars. Tank cars should contain all connections, a gauging device, thermometer, and a safety release valve within the car's dome. Ethylene oxide should be shipped in I.C.C. spec. 5P drums, I.C.C.-4B-400 cylinders (1 or 5 gal. size), or I.C.C.-105-AW tank cars. The tank car construction described for propylene oxide is suitable. The drum is a double walled insulated steel construction of approximately 260 pounds capacity. Its working pressure is 50 psig and it has a pressure relief valve set at 70 psig (Jefferson Chemical Co., undated a,b; Oxirane, undated).

Ethylene oxide and propylene oxide should be stored in areas that are well ventilated and protected from heat. Both are volatile, flammable and reactive. Ordinary carbon steel tanks are adequate. Some polymerization can occur during storage, which could subsequently foul valves and other equipment. Thus, storage facilities should have access for cleaning (Jefferson Chemical Co., undated a,b). As for other organic chemicals, the epoxides should be kept, if possible, in outside storage and away from combustible materials.

3. Accident Procedure

The potential hazards of spilled ethylene oxide or propylene oxide primarily stems from its fire or explosion potential. The primary response action should eliminate these hazards. Health hazards include possible inhalation toxicity, pollution of water supplies and in case of fire, the production of more toxic gases (DOT, 1974; ChemTrec, 1971). The recommended response to spills first addresses the fire hazard of these solvents: eliminate all sources of fire; stop leak if it is without risk; and reduce vapors with water spray. Large spills should be diked and small spills can be adsorbed with a noncombustible sorbent. The runoff should be kept from entering a sewer to avoid possible fire or explosion hazards.

Fires of liquid ethylene oxide are difficult to extinguish; it requires diluting the liquid 22:1 with water.

Vapor fires can be controlled with dry powders, vaporizing liquids, carbon dioxide, special alcohol-type air foam (not protein foam), and water fog.

Since ethylene oxide fires can lead to explosions, it is recommended that fires be isolated from other combustibles. Massive fires in cargo areas should be fought with unmanned hose holder or monitor nozzles. Storage equipment should be cooled with water spray.

V. EXPOSURE AND EFFECTS POTENTIAL

Since insufficient quantitative information was available on the selected epoxides in the environment, the exposure risk assessment is based upon qualitative information and upon hypothetical arguments. The exposure risk considers epoxide from manufacturing and from inadvertent sources. The evidence at hand suggests the bulk of manufactured epoxide does not create exposure risk. The majority of the epoxides are consumed in intermediate use in synthesis and relatively minor amounts are released. The risk of direct human exposure appears greatest with (1) medical devices, foodstuffs, and other products treated with ethylene or propylene oxide; (2) chlorinated solvents containing butylene oxide as a stabilizer; and (3) epoxides from inadvertent, nonmanufactured sources, in particular, from fuel combustion and cigarette smoke.

There is no evidence that epoxide exposure through water is significant. Epoxides have been identified in some industrial effluents (see Section II.E) but are not common constituents of effluents (Shackelford and Keith, 1976) and the epoxides degrade fairly fast (two weeks or less) (see Section II.D).

Sparse data exists on atmospheric emissions of the epoxides. The hypothesized possibilities discussed herein are based primarily on the processes for manufacture, handling, and use of the selected epoxides. None of the epoxides have been reported in analysis of plant effluents. Since at ambient temperature ethylene oxide is a gas and propylene oxide is a volatile liquid, fugitive emissions from industrial processing equipment, equipment cleaning, gauges, etc. are expected within the plant. Transfer of the materials would release only small amounts, if adequate precautions were adopted. If poor handling practices were applied during routines such as transfer from a transport tank to a storage tank, an epoxide emission of large size might result. Such an emission would create an occupational exposure risk. Risk to populations near a plant which manufacture or use an epoxide in synthesis is not clear. Little evidence is available on the atmospheric emissions of the epoxides or their exposure to nearby populations.

An accident, spill, or problem in transport, storage, or processing could, of course, release hazardous quantities. Available information on epoxide properties (physical, chemical, and biological reactivity) suggest that atmospheric degradation is relatively fast, which limits the geographic range and time of human exposure hazard.

The application of ethylene oxide and propylene oxide as fumigants or sterilants are the only uses which have been clearly associated with a significant human exposure. Less than 0.1 million pounds of ethylene oxide and even less of propylene oxide are applied for these purposes. The hazard from exposure through commodities are considered minimal. The epoxides are rapidly dissipated by volatilization and degradation. Although an unusual set of circumstances could create an incident of exposure by this route, all available information suggests that no problem exists under typical application and use conditions. Exposure to ethylene oxide through treated medical devices appears a more hazardous route. Health effects have been associated with devices implanted into humans (see below), but it is not certain if the toxic effect resulted from ethylene oxide or its metabolite ethylene chlorohydrin. Levels of ethylene oxide and its metabolites in medical products are regulated (see Section IV.A.1).

Butylene oxide's chief use is in chlorinated solvents as a stabilizer. Exposure to this epoxide is associated with use of these solvents. If precautions are utilized in the use and handling of chlorinated solvents, then exposure to butylene oxide is also minimized.

The epoxides are also inadvertently produced during combustion. They enter the environment through burning of fuel in stationary sources and from automobile exhaust. The amounts produced have not been quantified, but it was estimated that several million pounds of ethylene oxide and propylene oxide could be emitted through these combustion sources (see Section II.C.3). The general population would be at risk of exposure and exposure risk would be greatest near areas of high traffic or stationary emission sources.

Ethylene oxide has been identified as a component of cigarette smoke (see Section II.C.3). Tobacco fumigated with ethylene oxide appears to generate greater concentrations of ethylene oxide in the smoke; untreated, fumigated, and extensively fumigated tobacco yielded 0.02, 0.05, and 0.5 μg ethylene oxide per ml, respectively. Filtered cigarettes produced less ethylene oxide. The population at risk includes those exposed to side-stream smoke as well as the smoker.

The epoxides show potential health effects through their ubiquitous reactivity with functional groups of DNA, RNA, and proteins. Diepoxybutane, based on acute toxicity studies in animals, shows the highest reactivity of the compounds studied. This is further confirmed in mutagenicity studies carried out in animals, plants, and microorganisms, and carcinogenic activity noted in bioassays.

Most of the available published work regarding health effects of these epoxides deals with ethylene oxide. Occupational studies and clinical reports indicate that clothing articles (rubber shoes, rubber gloves, surgical gowns) sterilized with ethylene oxide can produce skin burns and blisters (Royce and More, 1955; Biro et al., 1974). These effects could be prevented by adequate ventilation of sterilized materials before use (Taylor, 1977c).

Hemolysis and anaphylactic reactions have been reported after the use of plastic medical devices sterilized with ethylene oxide (Hirose et al., 1953; Poothullil et al., 1975). Balazs (1976) estimated that ethylene oxide-sterilized plastic devices in prolonged contact or multiple use situations could release levels of compound well in excess of a theoretical no-effect level of 2.1 mg/day. This level is based on calculations of a 3 mg/kg (subcutaneous) no-effect level for ethylene oxide administered for 30 days to dogs. Use of a factor of 100 then leads to a derived safe level of 0.03 mg/kg or 2.1 mg for a 70 kg man. Further data concerning levels of release of ethylene oxide from sterilized plastic devices in vivo needs to be evaluated in order to assess the magnitude of this type of exposure. 2-Chloroethanol, a more persistant residue in these devices, may be formed after ethylene oxide sterilization; this compound has demonstrated mutagenicity in microbial systems (Rosenkranz et al., 1974).

Health effects in workers exposed to ethylene oxide vapor (ethylene oxide production plants, ethylene oxide sterilizer equipment) indicate neurological effects (Jensen, 1977), reproductive effects (Yakubova et al., 1976), chromosomal effects (Ehrenberg and Hallstrom, 1967), and an increased incidence of leukemia (Hogstedt et al., 1979). Animal studies with ethylene oxide confirm these classes of human effects: positive dominant lethal assay in mice, testicular atrophy in guinea pigs, teratogenicity in mice, chromosomal breaks in rats, and mutagenicity in a variety of microbial and plant systems. Ehrenberg and coworkers (1974) calculated that workers exposed to daily levels of 5 to 10 ppm ethylene oxide gas recieve the mutagenic equivalent of 4 to 8 rads gonadal dose of radiation weekly. If this estimate is correct, then long-term effects in workers exposed to ethylene oxide gas should be evaluated, particularly in women of child bearing age. The Veterans Administration and NIOSH are currently initiating separate studies covering large worker populations exposed to ethylene oxide gas.

Exposure to ethylene oxide residues in foods and spices sterilized with this compound involves levels considerably lower than those from sterilized medical devices. Based on the mutagenicity and possible carcinogenicity of ethylene oxide, further evaluation of the effects of extremely low levels of ethylene oxide exposure following ingestion seems appropriate.

VI. TECHNICAL SUMMARY

Four epoxides were studied: ethylene oxide; propylene oxide; butylene oxide; and diepoxybutane. Chemically, the epoxides are ethers which are characterized by the three membered oxygen-containing ring. They are slightly lower boiling and more reactive with acids and nucleophiles than are the analogous acyclic ethers. Ethylene oxide is a gas at ambient temperature and propylene oxide is a low boiling liquid (boiling point 34°C). The other epoxides are liquids (see Section I).

Ethylene oxide is among the leading chemicals in current production. For 1977 its production was estimated at 4,423 million pounds. It was primarily consumed in ethylene glycol manufacture (63%) and manufacture of polyols, polyol and glycol ethers, and ethanolamines (20 to 25%). Propylene oxide production in 1977 was estimated at 1,897 million pounds. It is mainly consumed in manufacture of polyurethane polymers (55%). It is also a feedstock for propylene glycol (20%), and various polyols (non-urethane), polyol ethers and glycol ethers (13%). Relatively small amounts of propylene oxide and ethylene oxide (less than 0.1 million pounds of each) are consumed as sterilants or pesticides for a variety of commodities, medical devices, cosmetics, and pharmaceuticals. Butylene oxide production has been decreasing from 9.5 million pounds in 1974 to an estimated 1.5 million pounds in 1980. It is primarily used as a stabilizer for chlorinated solvents. Diepoxybutane is a specialty chemical with an assumed annual production of less than 1000 pounds (see Section II.A and II.B).

Ethylene oxide is manufactured by catalytic oxidation of ethylene although a small amount is still manufactured by the older chlorohydrin route. Currently, propylene oxide is prepared by chlorohydrination or peroxidation of propylene, but new methods of catalytic oxidation, which have recently been developed, appear competitive. Butylene oxide is prepared by peroxidation or catalytic vapor phase oxidation of butylene. Diepoxybutane is synthesized from butadiene by chlorohydrination or an analogous method (see Section II.A.3).

Information was sparse on atmospheric release of manufactured epoxides. The available information indicates that only a small percentage of manufactured ethylene oxide and propylene oxide enters the environment. Because annual epoxide production is so large, even a small fraction of the total could result in several hundred thousand pounds of emissions. Pervier and coworkers (1974) surveyed ethylene oxide manufacturing plants and estimated that 118.6 million pounds of hydrocarbons were annually discharged; discharge was primarily vent loss. They noted that the discharge primarily consisted of ethylene; ethylene oxide release was not mentioned. Some losses are expected from fugitive emissions, ventings (especially during distillation), transfer and handling, spills, etc., but amounts are not known. Dow Chemical (Kurginski 1979) has indicated that the hydrocarbon loss figure is at least 20 times too high and ethylene oxide annual loss from production and processing is less than 5 million lbs. A report of ethylene oxide in chemical plant effluent (Shackelford and Keith, 1976) was the only monitoring data concerning waste-related epoxide release. No information on propylene oxide release to the environment was available. Butylene oxide, which is added to chlorinated solvents, will share the fate of the solvent; losses to the atmosphere are expected.

The application of ethylene oxide and propylene oxide to consumer commodities and other items as sterilant or pesticide creates the possibility of human exposure. The epoxide and its residues (halohydrins and glycols) have been identified in treated products including food (Wesley _et_ _al_., 1965), drugs (Holmgren _et_ _al_., 1969), and medical devices (Brown, 1970). In fact, human health effects were traced to surgically implanted devices that were treated with ethylene oxide (see below). The extent of this exposure is unknown because of the limited monitoring data that is available.

The monoepoxides (ethylene, propylene, and butylene oxide) can be inadvertently produced through a variety of sources. They are known products of atmospheric oxidations (Sato and Cvetanovic, 1958; Altshueller and Buffalini, 1965). They have also been observed as products of partial combustion of fuels (Hughes _et al_., 1959) and in automotive exhaust (Barnard and Lee, 1972); epoxides emitted from these sources may approach millions of pounds annually. Ethylene oxide has been measured in cigarette smoke, the amount depending in part upon fumigation of the tobacco with ethylene oxide (Binder, 1974). While unfumigated tobacco yielded smoke with an ethylene oxide concentration of 0.02 μg/ml, in extensively fumigated tobacco its concentration was 0.3 μg/ml (see Section II.C.7).

The epoxides degrade in the environment. In water they react by chemical hydrolysis and with anions such as chloride and carbonate (Brönsted _et al_., 1929; Ross, 1950). Although intermediates form (such as chlorohydrins from epoxide reaction with chloride), glycols are the terminal products. Half-lives were calculated for aqueous degradation in ambient conditions (pH 7 and 25°C) in fresh water and in sea water (0.57 _M_ chloride) as follows: ethylene oxide - 2 weeks in fresh water and 4 days in sea water and propylene oxide - 12 days in fresh water and 4 days in sea water. These half-lives do not account for biodegradation routes. The only information available on epoxide degradation in soil described metabolic transformations, which parallel chemical hydrolysis and reaction with anions. Rate factors for the metabolic processes were not available (Castro and Bartnicki, 1968; Bartnicki and Castro, 1969). Atmospheric degradations of the epoxides have not been directly studied.

Since the information available on their free-radical reactions describe their reactivity as similar to acyclic ethers and to other cyclic ethers, the epoxides probably degrade very rapidly (Darnall et al., 1976). Epoxides applied as sterilants or pesticides for commodities and other items dissipate through a combination of volatilization and degradation (Scudamore and Heuser, 1971; Stijve et al., 1976). Storage in closed containers will stop the volatilization loss. The epoxide degradation pathways parallel the chemical degradation described above. If inorganic halide (chloride or bromide) is present, then halohydrins form. Reaction of epoxide or halohydrins with water yields glycol (see Section II.C).

Physical properties of the epoxides suggest that they are very mobile and do not bioaccumulate. Their high water solubility precludes any capacity to bioconcentrate. Solubility factors also suggest potential for transport with surface or ground water. Since ethylene oxide and propylene oxide possess high vapor pressures, they will volatilize readily (Alguire, 1973). There was no information available concerning transport between air and water. It is not certain which media is most important in the fate of the epoxides.

The toxic effects of human exposure to ethylene oxide and propylene oxide appear to be quite similar (Hine and Rowe, 1973). Based on animal toxicity studies, propylene oxide is one-half to one-third as acutely toxic as ethylene oxide (Jacobsen et al., 1956). Systemic poisoning following accidental exposure to high ethylene oxide concentrations has produced symptoms of headache, vomiting, dyspnea, diarrhea, and lymphocytosis (Sexton and Henson, 1949). Thiess (1963) reported that accidental brief exposure to high concentrations of ethylene oxide vapor has produced bronchitis, pulmonary edema, and emphysema in workers. Dermatitis has resulted from contact with ethylene oxide, producing large characteristic blisters (Taylor, 1977). Sensitization to ethylene oxide has been described by Dolovich et al. (1978), and anaphylactic reactions to ethylene oxide residues in medical devices has also been reported (Pessayre and Trevoux, 1978; Poothullil et al., 1975). Clinical reports of hemolysis following usage of ethylene oxide sterilized plastic tubing have also been published (Hirose et al., 1953). Conjunctivitis and corneal burns have been produced by exposure to high levels of ethylene oxide and propylene oxide (McLaughlin, 1946); these effects may be reversible within a few days.

Three incidences of lower limb neuropathy in workers using ethylene oxide sterilizers were reported by Jensen (1977); a followup indicated that these effects were reversible.

Epidemiological studies on ethylene oxide exposure have produced varied findings. Joyner (1964) was unable to show significant adverse health effects in an investigation of workers exposed for five to sixteen years in an ethylene oxide production plant. A preliminary study of health records of employees in 162 Veterans Administration hospitals and seven clinics using ethylene oxide sterilizers failed to show any effects other than watering eyes, nausea, and skin irritation (NIOSH, 1977). A followup of this survey is planned. A study by Ehrenberg and Hallstrom (1967) of 251 Swedish workers in an ethylene oxide production facility found three cases of blood cell anisocytosis and one case of leukemia. Workers exposed to high (accident) ethylene oxide concentrations showed greater numbers of chromosomal aberrations. A follow up of this study is also planned.

Recently, a study of 230 Swedish workers exposed to a mixture of ethylene oxide and methyl formate gas in a storage hall containing gas-sterilized boxes has shown the development of three cases of leukemia with latencies of 4 years, 6 years, and 8 years, respectively (Hogstedt et al, 1979). This is considerably higher than the projected incidence rate of 0.2 cases for this population. Workers were exposed to an assumed concentration of 20 ± 10 ppm ethylene oxide over a nine-year period, but concentrations in the storage hall could have reached levels of approximately 150 ppm or higher.

Yakubova and coworkers (1976) reported that pregnant workers in ethylene oxide production facilities were prone to miscarriages and toxicosis in the second half of pregnancy. Levels of exposure and quantitation of effects were not available for analysis. Neither the study by Joyner nor the study conducted by Ehrenberg and Hallstrom involved any female participants.

The acute toxicity of epoxides in animal studies indicates that diepoxybutane shows high acute toxicity (LD_{50} in the mouse after i.p. injection, 16 mg/kg; Weil, 1963), followed in decreasing order by ethylene oxide, propylene oxide, and butylene oxide. Comparative acute toxicity of ethylene oxide administered by inhalation demonstrates that mice and dogs seem most susceptible while rats and guinea pigs appear less sensitive.

Animal studies with radioactively labelled ethylene oxide have indicated that after injection this compound may be found in tissues throughout the body including the liver, kidneys, lungs, pancreas, epididymis, testes, and cerebellum (Appelgren et al., 1977). The major portion of absorbed ethylene oxide is metabolized rapidly and excreted. Eighty percent of the labelled compound in animals exposed by inhalation was found in the urine within 48 hours (Ehrenberg et al., 1974). Tissue components alkylated in vivo by ethylene oxide may represent the remainder of compound absorbed.

Ethylene oxide inhalation has produced bone marrow effects in several species of animals. Jacobsen and coworkers (1956) noted a decrease in red blood cell count, hemoglobin, and hematocrit in dogs exposed for 6 hrs/day to 292 ppm ethylene oxide for six weeks. Woodward and Woodward (1971) determined that dogs injected s.c. for 30 days with 6 to 36 mg/kg ethylene oxide developed anemia and showed bone marrow hyperplasia. Increased chromosomal aberrations (breaks, rings, gaps, bridges) have been observed in rats treated with ethylene oxide (Embree and Hine, 1975; Strekalova, 1971). Appelgren and coworkers (1978) noted bone marrow depression and increased red blood cells with micronuclei in rats injected twice i.v. with ethylene oxide at the level of 100 mg/kg.

Diepoxybutane showed effects on mouse sperm chromosomes 24 hours after i.p. injection at 5 mg/kg (Moutschen, 1961). This exposure included increased chromosome breaks and anaphase bridges.

Reproductive effects have been seen in animals, including degeneration of the testicular tubules of guinea pigs following inhalation of ethylene oxide (Hollingsworth et al., 1956) and a positive dominant lethal assay in rats (Embree and Hine, 1977). Epstein and coworkers (1972) reported that i.p. injection of 17 mg/kg of diepoxybutane into mice produced an increase of early fetal deaths in the dominant lethal assay.

Neurotoxic effects were observed in mice, rats, and monkeys exposed repeatedly (33 to 94 times) to 357 ppm ethylene oxide inhalation (Hollingsworth et al., 1956). Paralysis and atrophy of the hind-limb muscles developed, and impairment of sensory and motor function at the sacral and lumbar regions of the spinal chord was inferred. Reversal of paralytic symptoms in rats and mice was seen in 100 to 132 days after exposure was stopped.

The epoxides have been shown to produce mutagenic effects in a wide variety of plant and microbial systems. Positive results in the Ames mutagenicity assay have been seen with ethylene oxide (Rannug et al., 1976; Taylor, 1979; Embree and Hine, 1975; Kauhanen, 1977) without the addition of microsomal activation mix. Taylor (1979) showed that addition of microsomal activation enzymes (S-9 mix) increases the number of mutants produced in tester strains TA1535 and TA100 at ethylene oxide vapor concentrations from 10 ppm to 100 ppm.

Propylene oxide increases mutations in tester strains TA100 and TA1535 at the level of 1 to 1.5 mg/plate without activation (Wade et al., 1978).

Diepoxybutane exhibited mutagenic activity in the Ames assay without activation (McCann et al., 1975; Rosenkranz and Poirer, 1979; Simmon, 1979). Rosenkranz and Poirer (1979) showed that the increase in mutations induced by diepoxybutane in tester strains TA1535 and TA1538 is partially eliminated if microsomal activation mix is added.

Butylene oxide also showed positive activity in the Ames assay. Speck and Rosenkranz (1976) reported increased mutants in tester strains TA 100 without activation following application of 14 ug of compound. Positive Ames assay results have also been reported by others (Chen et al., 1975; Rosenkranz and Speck, 1975; Rosenkranz and Poirer, 1979).

Diepoxybutane and ethylene oxide have both induced mutations at the adenine locus of *Neurospora* (Kolmark and Westergaard, 1953) and to increase several types of mutations in barley seeds (Ehrenberg and Gustaffson, 1957). Ehrenberg has estimated that diepoxybutane is 200 times more active than ethylene oxide in producing this effect in barley. Both ethylene oxide and diepoxybutane increase the incidence of lethal mutations after injection in *Drosophila* (Bird and Fahmy, 1953).

Simmon (1979b) showed increased mutations in Saccharomyces following exposure to 0.6% butylene oxide; inclusion of microsomal activation mix reduced the number of mutations observed.

Teratogenic effects have been observed following injection of ethylene oxide into rats during gestation (Kimmel and Laborde, 1979). Doses of 150 mg/kg of ethylene oxide injected daily for three days at different times during gestation increased fetal malformations when injected at days 6 to 10 of gestation. Chloroethanol, a potential reaction product of ethylene oxide, produced fetal malformations after injection into the air sack of chick embryos (Versett, 1974).

Carcinogenic effects were reported after exposure of test animals to ethylene oxide, propylene oxide, and diepoxybutane. Reyniers and coworkers (1964) noted ovarian, lymphoid, and pulmonary tumors in female germ-free mice exposed to ethylene oxide-treated corncob bedding. No chemical analysis of the bedding was carried out, so the implication of ethylene oxide involvement is circumstantial. Colony mates raised on nontreated bedding did not develop tumors. Both Van Duuren et al. (1965) in skin painting studies on mice, and Walpole (1958) in injection studies on rats, were unable to demonstrate increased tumors from ethylene oxide exposure. Walpole (1958) reported that eight rats injected subcutaneously with a total dose of 1.5 mg/kg of propylene oxide over 325 days developed tumors in 507 to 739 days (schedule not indicated).

Diepoxybutane has been shown to produce tumors following skin painting (McCammon et al., 1957; Weil et al., 1963; Van Duuren et al., 1966; Shimkin et al., 1966), and to act as a tumor initiating agent in mouse skin (Van Duuren, 1969). Butylene oxide applied for 540 days (3 times weekly) at the level of 100 mg to mouse skin did not produce tumors (Van Duuren et al., 1967).

The epoxides have produced neurotoxic effects, reproductive effects, and bone marrow effects, and have demonstrated mutagenicity, teratogenicity, and carcinogenicity. Exposure of humans to these compounds should therefore warrant caution. Long-term effects from low-level exposure of these compounds have not been well characterized; this type of exposure and consequent effects appear to be very pertinent to human exposure and risk. Industry is sponsoring inhalation studies on ethylene oxide (complete by summer 1980) and propylene oxide (complete by summer 1982) (Kurginski, 1979).

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CONCLUSIONS AND RECOMMENDATIONS

From the preceeding literature review and evaluation the following conclusions and recommendations seem justified.

1. Ethylene oxide (EO) and propylene oxide (PO) are produced and consumed in very large quantities (estimated at 4,423 million pounds and 1,897 million pounds, respectively, in 1977). They are primarily consumed as synthetic intermediates and in polymer production.

2. Butylene oxide is produced and used in a moderate amount (ca. 9.5 million pounds in 1974) but the current trends indicate that commercial production and use will fall to 1.5 million pounds in 1980. It is primarily consumed as a scavanger in chlorinated solvents.

3. Diepoxybutane is produced in insignificant quantities.

4. At ambient temperature EO is a gas and PO is a volatile liquid, so potential exists for their release to the environment.

5. Insufficient information currently exists on the atmospheric release of EO and PO during manufacture and use for chemical synthesis and in polymer manufacture. Specific evaluation of all modes of environmental release of EO and PO should be performed.

6. Relatively small amounts of EO and PO are applied as a fumigant or sterilant to a wide variety of consumer items (less than 0.1 million pounds per year for EO and even less for PO), which include food commodities, medical devices, pharmaceuticals, and cosmetics. This use of EO and PO created the only documented human exposure from the manufactured product other than accidental occupational exposure. The extent of this exposure needs to be documented.

7. EO and PO are products of partial combustion and have been identified in automotive exhaust, roasted foods, and tobacco smoke (inhaled and side stream). EO appeared in smoke from tobacco which was not fumigated with EO, but if tobacco was so fumigated, the EO concentration of the smoke increased.

8. The epoxides show a wide range of mutagenic effects. Mammalian mutagenic effects need to be confirmed in experiments involving administration of the compounds by routes relevant to human exposure - i.e., dermal, oral, and inhalation routes. Diepoxybutane and other reactive epoxides have been shown to have tumorigenic activity.

9. The carcinogenic activity of ethylene oxide, propylene oxide, and butylene oxide should be further evaluated, as well as the teratogenic activity of these same compounds.

10. Long term effects of neurotoxicity, chromosome aberrations, reproductive effects, and leukemia in workers exposed to ethylene oxide have been reported. The incidence and reversibility of these effects in human populations needs to be defined. Similarly, long term effects from indwelling or repeated usage of plastic medical devices sterilized with ethylene oxide needs evaluation. Effects of human exposure to butylene oxide and diepoxybutane have not been reported.